

Clinical and Economic Burden of Intravenous Paclitaxel or nab-Paclitaxel for Metastatic Breast Cancer

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Introduction

In 2020, an estimated 279,100 women will be newly diagnosed with breast cancer (BC) in the United States, representing 30.5% of all new cancer diagnoses in women.¹ Among this group, about 6% have distant metastases at diagnosis (mBC)²; the remainder of women with mBC experience progression from earlier-stage BC.^{3,4} While the overall mortality rate for BC has decreased by 40% since 1989,³ it remains the leading cause of death for women aged 45 to 64 years, as estimated 5-year relative survival for mBC is only 27%.^{1,5}

Despite improvements in detection and treatment, mBC remains incurable; therapy aims to ameliorate symptoms, delay disease progression, and improve quality of life and survival.⁶ Intravenous (IV) taxanes (paclitaxel, nab-paclitaxel, docetaxel) have been foundational BC treatments for the last 3 decades.^{7,8} Despite the efficacy of taxanes in extending survival, many patients experience dose-limiting adverse effects (AEs) including infusion reactions, chemotherapy-induced peripheral neuropathy (CIPN), and myeloid cytopenia.^{7,9}

Further, management of BC is associated with high health care costs.^{10,11} Costs vary by stage, with mBC patients incurring the highest costs of care, estimated at \$134,682 per patient in the year following diagnosis; cumulative costs are estimated at \$270,033 to \$588,491 for patients who survive ≥ 3 years after mBC diagnosis.^{10,12} Chemotherapy is the primary cost driver^{10,13}; however, correlations have been reported between treatment-related toxicities and higher health care costs.^{14,15}

Although some data exist on the economic burden of mBC, limited data are available on the specific costs of care with IV paclitaxel and IV nab-paclitaxel treatment.^{14,16} This observational, retrospective study used administrative claims data to examine treatment patterns, toxicities, health care resource utilization (HCRU), and health care costs among women with mBC initiating treatment with IV paclitaxel or IV nab-paclitaxel.

Methods

Data Source

This observational retrospective analysis utilized the deidentified IBM MarketScan Commercial Claims and Encounters (commercial) and MarketScan Medicare Supplemental (Medicare) administrative claims databases for the period November 1, 2012, to December 31, 2018. The commercial database contains the inpatient, outpatient, and outpatient prescription drug experience of employees and their dependents, covered under a variety of health plans. The Medicare database contains the full health care experience (both medical and pharmacy) of retirees with Medicare supplemental insurance provided by employers; Medicare and employer covered portions of payments are included.

All study data were obtained using National Drug Codes and codes from *International Classification of Diseases, Clinical Modification*, 9th and 10th revisions (*ICD-9-CM* and *ICD-10-CM*); from Current Procedural Terminology, 4th edition; and from Healthcare Common Procedure Coding System.

Patient Selection and Study Periods

Women with ≥ 1 inpatient or ≥ 2 nondiagnostic outpatient claims with a diagnosis of BC (*ICD-9-CM*: 174.xx; *ICD-10-CM*: C50.xx) from January 1, 2014, through September 30, 2018, were identified within the MarketScan databases. Women were also required to have ≥ 1 nondiagnostic claim with a diagnosis of metastasis occurring 60 days prior to the first BC claim through the end of data (excludes codes for metastasis to the breast) and ≥ 1 claim for IV paclitaxel or IV nab-paclitaxel (hereafter referred to as IV paclitaxel/nab-paclitaxel) in the outpatient medical setting following the diagnosis of metastasis. The index date was the date of first administration of IV paclitaxel/nab-paclitaxel.

Eligible women had to be ≥ 18 years on the index date and have continuous enrollment with medical and pharmacy benefits for ≥ 12 months prior (preperiod) to and ≥ 3 months following the index date. Patients who received

Abstract

BACKGROUND: Intravenous (IV) taxane therapy for metastatic breast cancer (mBC) has been associated with toxicities and demanding dosing schedules, which can limit treatment effectiveness.

OBJECTIVES: To assess treatment patterns, toxicities, and costs in women with mBC initiating IV paclitaxel or IV nab-paclitaxel.

METHODS: Adult women diagnosed with BC from January 1, 2014, to September 30, 2018, were identified in the MarketScan Commercial and MarketScan Medicare Supplemental databases. Women had a metastatic disease diagnosis and newly initiated treatment with IV paclitaxel/nab-paclitaxel (first administration date was considered the index date), and continuous enrollment for at least 12 months prior to and at least 3 months following the index date. Treatment discontinuation, dose reductions, toxicities, and health care utilization and costs per patient per month (PPPM) were assessed over the full follow-up and the index line of IV paclitaxel/nab-paclitaxel therapy (Index LOT).

RESULTS: The sample included 8890 women aged 54.6 (± 10.9) years, followed for 18.9 (± 13.5) months. Most (82.0%) initiated IV paclitaxel/nab-paclitaxel monotherapy; 83.1% had early discontinuation (< 18 weeks of treatment) of the Index LOT. Among the 6943 women eligible for the dose-change analysis, 42.4% evidenced an IV paclitaxel/nab-paclitaxel dose reduction $\geq 10\%$ during the Index LOT. The most common toxicities during the Index LOT were gastrointestinal upset (30.5%), myelotoxicity (27.0%), infection (26.2%), general symptoms (25.9%), and chemotherapy-induced peripheral neuropathy (22.7%). Over follow-up, 39.7% of women had an inpatient admission and 43.0% had an emergency department visit. The mean of all-cause total costs was \$11,991 PPPM, while BC-related total costs were \$5320 PPPM.

CONCLUSIONS: Many mBC patients initiating IV paclitaxel/nab-paclitaxel experienced dose reductions, toxicities, and/or early discontinuation of the Index LOT, which may limit treatment effectiveness. More tolerable treatments with reduced dosing complexity could improve mBC treatment and help contain costs.

KEY WORDS: metastatic breast cancer, chemotherapy treatment patterns, healthcare service utilization and costs

ETHICS APPROVAL AND INFORMED CONSENT

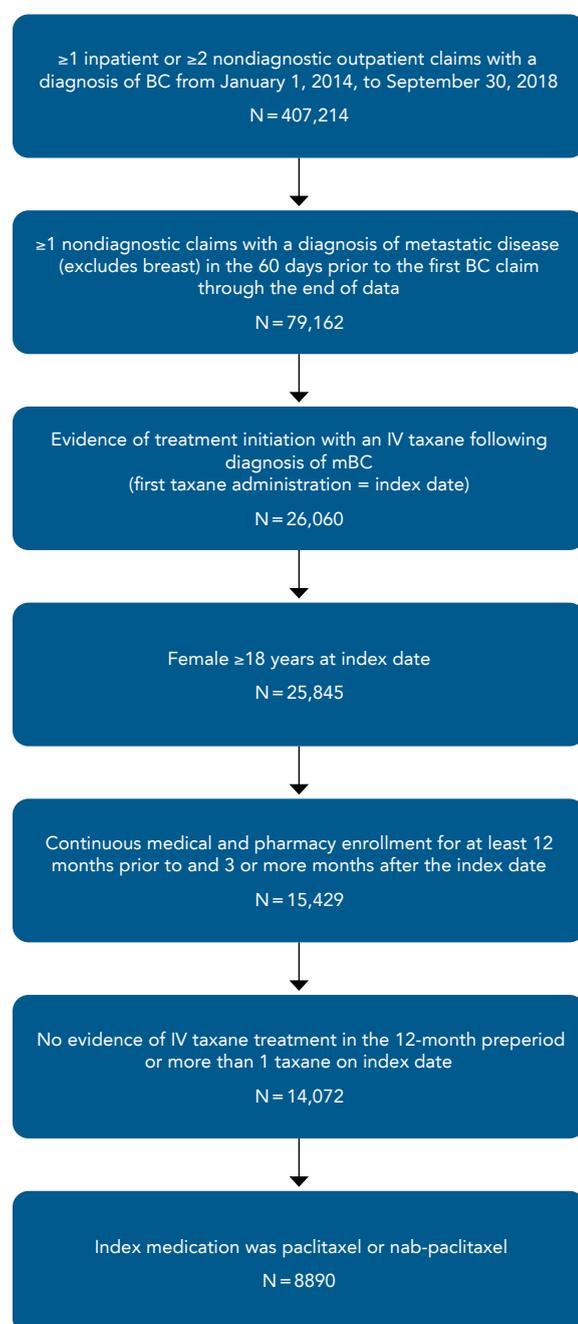
All database records are statistically deidentified and certified to be fully compliant with US patient confidentiality requirements set forth in the Health Insurance Portability and Accountability Act of 1996. Because this study used only deidentified patient records and did not involve the collection, use, or transmittal of individually identifiable data, this study was exempted from Institutional Review Board approval.

Take-Away Points

Early discontinuation, dose reductions, and toxicities are common among women with mBC initiating IV paclitaxel or IV nab-paclitaxel, and they may impact the effectiveness of treatment and long-term patient outcomes. Further, the economic burden among patients treated with IV paclitaxel or nab-paclitaxel is substantial at \$11,991 per patient per month, or approximately \$143,892 annually. Treatments with improved tolerability stand to improve the clinical burden for patients and economic burden on the health care system.

- 83.1% of women with mBC discontinued IV paclitaxel/nab-paclitaxel early, and 42.1% had a dose reduction.
- 78.6% of patients experienced a toxicity requiring medical attention while on IV paclitaxel/nab-paclitaxel.

FIGURE. Sample Attrition of Women With mBC Initiating IV Paclitaxel or IV nab-Paclitaxel



BC, breast cancer; IV, intravenous; mBC, metastatic breast cancer.

any IV taxane in the 12-month preperiod or >1 taxane on the index date were excluded (to isolate impact of paclitaxel). The variable follow-up period extended from index until the earliest of: (1) docetaxel administration; (2) end of continuous enrollment; or (3) end of the study period (December 31, 2018).

Lines of Therapy and Dose Changes

The first line of IV paclitaxel/nab-paclitaxel therapy, starting on the index date, was defined.

Index line of therapy (LOT) components included IV paclitaxel/nab-paclitaxel and all chemotherapy agents (capecitabine, carboplatin, cisplatin, cyclophosphamide, doxorubicin, epirubicin, eribulin, fluorouracil, gemcitabine, ixabepilone, methotrexate, and vinorelbine) administered in the 37 days following the index date. As patients may have been receiving nontaxane chemotherapy prior to the index date, the 37-day period allowed identification of concomitant medications that were administered on a different cycle. The end of the Index LOT was defined by a regimen change or the end of follow-up; medication discontinuation was defined as a gap in treatment of ≥ 45 days. For patients with a subsequent LOT during follow-up, the components of the second LOT were identified.

Changes in IV paclitaxel/nab-paclitaxel dose were assessed during the Index LOT. Dose was estimated by dividing the paid amount on IV paclitaxel/nab-paclitaxel claims by the wholesale acquisition cost; capitated claims, claims with a JW modifier (indicating medication waste), or a \$0 paid amount were excluded. To facilitate assessment of changes over time, only patients with ≥ 3 non-\$0 claims for IV paclitaxel/nab-paclitaxel were included in the dose analysis. The magnitude of a dose change was defined as $\geq 10\%$ of the index dose, and dose changes were examined in relation to the prior dose.

Patient Characteristics and Comorbidities

Demographics were measured on index. The National Cancer Institute (NCI) Comorbidity Index and treatment characteristics were examined during the preperiod.^{17,18} The prevalence and incidence of comorbidities were assessed during the Index LOT and full follow-up. Comorbidities included depression, diabetes, insomnia, falls, fractures, liver dysfunction, rheumatoid arthritis, and nonrheumatoid arthritis (osteoarthritis, psoriatic arthritis, and other polyarthropathies). Patients without a diagnosis of the comorbidity of interest in the preperiod were eligible for the incidence analysis.

Toxicities

Prevalent and incident toxicities were assessed over the Index LOT and the full follow-up; the incident

toxicity analysis included only patients without a diagnosis for the toxicity of interest during the preperiod. During the Index LOT, dose changes in the 14 days following a toxicity, and neuropathy medication use in the ± 10 days around a dose change, were both reported as proxies for toxicity-associated events. Over the full follow-up, hospitalizations or emergency department (ED) visits in the 14 days following an incident toxicity (temporal correlation) were assessed as a proxy for toxicity severity. Toxicities included alopecia, CIPN, cardiovascular events (angina, atrial fibrillation, atrial flutter, atrioventricular block, cardiac arrest, cardiac tamponade, disseminated intravascular coagulation, heart failure, myocardial infarction, stroke, thromboembolism, and thrombosis), cardiovascular symptoms (bradycardia, chest pain, and tachycardia), general AEs (fever, headache, malaise/fatigue, edema, fluid retention, epistaxis, and dysgeusia/dysosmia), gastrointestinal (GI) events (ascities, colitis, esophagitis, GI bleeding, GI obstruction, GI perforation, pancreatitis, and peptic ulcer), GI symptoms (constipation, dysphagia, and stomatitis), GI upset (abdominal pain, diarrhea, dyspepsia, and nausea/vomiting), hematological effects, infection, infusion-related/hypersensitivity effects, joint/muscle effects, musculoskeletal effects, myelotoxicity, nervous system effects (ataxia, dizziness, vertigo, syncope, and seizures), encephalopathy, neutropenia, paresthesias, pulmonary events, renal toxicity, and skin effects (full list in Supplemental Materials).

HCRU and Costs

All-cause and BC-related HCRU and costs per patient per month (PPPM), including inpatient admissions, outpatient medical encounters (ED visits, outpatient office visits, and other outpatient services), and outpatient prescriptions were reported over follow-up. BC-related HCRU included inpatient admissions with a diagnosis of BC in the primary position; outpatient services with a diagnosis of BC in any position; medical claims for BC treatments (chemotherapy, endocrine therapy, HER2-directed therapy, or radiation); pharmacy claims for BC; and pharmacy claims for medications prescribed to relieve neuropathy (antidepressants, anticonvulsants, opioids and narcotics, systemic corticosteroids, nonopioid and nonsteroidal pain relief drugs, topical local anesthetics, mexiletine, tocainide, and pentoxifylline). Costs represented the paid amounts of fully adjudicated claims; costs for capitated plans were estimated via payment proxy. All costs were inflated to 2019 US dollars using the medical care component of the Consumer Price Index.¹⁹

Statistical Analysis

Mean and SD were reported for continuous variables. Frequencies and percentages were reported for categorical variables. All data analyses were conducted using WPS version 4.1 (World Programming, United Kingdom).

Results

A total of 8890 women with mBC initiating treatment with IV paclitaxel/nab-paclitaxel qualified for the study (Figure). Mean age was 54.6 (± 10.9) years at index; mean NCI comorbidity score was 0.6 (± 1.0),

TABLE 1. Demographics and Preperiod Characteristics in Women With mBC Initiating IV Paclitaxel or IV nab-Paclitaxel

	IV paclitaxel/ nab-paclitaxel N = 8890	
	N/mean	%/SD
Age, years (mean, SD)	54.6	10.9
Insurance plan type		
Comprehensive/indemnity (N, %)	774	8.7%
EPO (N, %)	77	0.9%
HMO (N, %)	899	10.1%
POS (N, %)	629	7.1%
POS with capitation (N, %)	61	0.7%
PPO (N, %)	4707	52.9%
CDHP/HDHP (N, %)	1616	18.2%
Other/unknown (N, %)	127	1.4%
NCI Comorbidity Index (mean, SD)	0.6	1.0
Preindex breast cancer treatments		
Chemotherapy*		
Doxorubicin (N, %)	5309	59.7%
Cyclophosphamide (N, %)	5238	58.9%
Capecitabine (N, %)	510	5.7%
Gemcitabine (N, %)	230	2.6%
Carboplatin (N, %)	180.0	2.0%
Eribulin (N, %)	121	1.4%
Vinorelbine (N, %)	102	1.1%
Methotrexate (N, %)	87	1.0%
Endocrine therapy (N, %)	1654	18.6%
HER2-directed therapy (N, %)	223	2.5%
Number of preindex BC therapies (mean, SD) ^b	1.6	1.0
Number of preindex BC therapies (N, %) ^b		
0	1718	19.3%
1	838	9.4%
2	5481	61.7%
3+	853	9.6%
Radiation therapy (N, %)	1070	12.0%
BC-related surgery (N, %)	704	7.9%
Months of follow-up (mean, SD)	18.9	13.5
At least 12 months of follow-up (N, %)	5233	59.0%

BC, breast cancer; CDHP, consumer-driven health plan; EPO, exclusive provider organization; HDHP, high deductible health plan; HMO, health maintenance organization; IV, intravenous; mBC, metastatic breast cancer; NCI, National Cancer Institute; POS, point of service; PPO, preferred provider organization.

*Only regimens used by at least 1% of patients are reported.

^bIncludes cytotoxic chemotherapy, endocrine therapy, and HER2-directed therapy.

and patients were followed for a mean of 18.9 (\pm 13.5) months (Table 1).

Treatment Characteristics

The most common preperiod chemotherapies were doxorubicin (59.7%) and cyclophosphamide (58.9%; Table 1). Endocrine therapy was used by 18.6% of patients; 2.5% of patients utilized HER2-directed therapy. More than 80% of

TABLE 2. Treatment Characteristics and IV Paclitaxel/nab-Paclitaxel Dose Changes During the Index LOT in Women With mBC Initiating IV Paclitaxel or IV nab-Paclitaxel

	IV paclitaxel/ nab-paclitaxel N = 8890	
	N	%
Index LOT characteristics		
Taxane initiated		
IV paclitaxel (N, %)	7714	86.8%
IV nab-paclitaxel (N, %)	1176	13.2%
Endocrine therapy (N, %)	1043	11.7%
HER2-directed therapy (N, %)	1091	12.3%
Duration of LOT, months (mean, SD)	3.2	2.1
Reason for end of LOT		
Augmentation or switch (N, %)	1255	14.1%
Drop (N, %)	6864	77.2%
End of follow-up (N, %)	771	8.7%
Evidence of early discontinuation (N, %)	7384	83.1%
Dose changes		
Patients eligible for dose-change analysis (N, %)	6943	78.1%
Patients with a dose change \geq10% (N, %)	3497	50.4%
Number of dose changes (mean, SD)	2.0	1.8
Time to dose change, days (mean, SD)	39.4	38.3
Patients with a dose reduction \geq10% (N, %)	2945	42.4%
Number of dose reductions (mean, SD)	1.5	1.0
Time to earliest dose reduction, days (mean, SD)	46.1	41.7
First reduction as proportion of prior dose (mean, SD)	0.7	0.2
>80% (N, %)	950	32.3%
50%-80% (N, %)	1407	47.8%
<50% (N, %)	588	20.0%
Patients with 2+ dose reductions (N, %)	847	28.8%

(continued >)

*See supplemental materials for specific toxicities in each category.

^bGeneral symptoms included fever, headache, malaise/fatigue, edema, fluid retention, epistaxis, and dysgeusia/dysosmia.

CIPN, chemotherapy-induced peripheral neuropathy; CVD, cardiovascular disease; GI, gastrointestinal; IV, intravenous; LOT, line of therapy; mBC, metastatic breast cancer; POS, point of service.

women received \geq 1 systemic BC therapy during the preperiod.

Most patients (86.8%) initiated IV paclitaxel on the index date; the remaining 13.2% initiated IV nab-paclitaxel (Table 2). Overall, 82.0% of patients received IV paclitaxel/nab-paclitaxel monotherapy. Among the 1596 patients who received polytherapy (combination with IV paclitaxel/nab-paclitaxel), carboplatin (62.8%), cyclophosphamide and

	IV paclitaxel/ nab-paclitaxel N = 8890	
	N	%
Dose change proxies		
Evidence of neuropathy medication within \pm 10 days of dose reduction (N, %)	1157	39.3%
Evidence of dose reduction within 14 days after toxicity^a (N, %)	1626	55.2%
Alopecia (N, %)	0	0.0%
CIPN (N, %)	371	12.6%
CVD event (N, %)	91	3.1%
CVD symptom (N, %)	77	2.6%
General symptoms ^b (N, %)	254	8.6%
GI events (N, %)	39	1.3%
GI symptoms (N, %)	49	1.7%
GI upset (N, %)	548	18.6%
Hematological (N, %)	37	1.3%
Infection (N, %)	230	7.8%
Infusion-related/hypersensitivity effects (N, %)	59	2.0%
Joint/muscle effects (N, %)	91	3.1%
Musculoskeletal effects (N, %)	79	2.7%
Myelotoxicity (N, %)	432	14.7%
Nervous system effects (N, %)	38	1.3%
Encephalopathy (N, %)	0	0.0%
Neutropenia (N, %)	357	12.1%
Paresthesias (N, %)	25	0.8%
Pulmonary event (N, %)	97	3.3%
Renal toxicity (N, %)	21	0.7%
Skin effects (N, %)	20	0.7%

doxorubicin (13.5%), and gemcitabine (7.5%) were the most common other therapy components.

Treatment Changes Over the Index LOT

The duration of the Index LOT was 3.2 (\pm 2.1) months; 77.2% of patients ended their Index LOT due to discontinuation of \geq 1 regimen medication. Considering that 82.0% of the patients received monotherapy for the Index LOT, IV paclitaxel/

TABLE 3. Incident Toxicities Among Women With mBC Who Initiated Treatment With IV Paclitaxel or IV nab-Paclitaxel

	Index LOT IV paclitaxel/nab-paclitaxel N = 8890		Full follow-up IV paclitaxel/nab-paclitaxel N = 8890	
	N/Rate	%	N/Rate	%
Alopecia				
Patients without alopecia in preperiod (N, %)	8863	99.7%	8863	99.7%
Patients with alopecia (N, %)	9	0.1%	24	0.3%
Incidence rate per 100 person-years	0.4		0.2	
Inpatient admission or ED visit within 14 days of event (N, %)	1	11.1%	2	8.3%
CIPN				
Patients without CIPN in preperiod (N, %)	6578	74.0%	6578	74.0%
Patients with CIPN (N, %)	1247	19.0%	3121	47.4%
Incidence rate per 100 person-years	79.4		49.7	
Inpatient admission or ED visit within 14 days of event (N, %)	128	10.3%	372	11.9%
CVD events				
Patients without CVD events in preperiod (N, %)	7861	88.4%	7861	88.4%
Patients with CVD events (N, %)	385	4.9%	1127	14.3%
Incidence rate per 100 person-years	18.9		9.8	
Inpatient admission or ED visit within 14 days of event (N, %)	198	51.4%	611	54.2%
CVD symptoms				
Patients without CVD symptoms in preperiod (N, %)	7095	79.8%	7095	79.8%
Patients with CVD symptoms (N, %)	425	6.0%	1545	21.8%
Incidence rate per 100 person-years	23.5		16.0	
Inpatient admission or ED visit within 14 days of event (N, %)	241	56.7%	820	53.1%
General symptoms^a				
Patients without general symptoms in preperiod (N, %)	5859	65.9%	5859	65.9%
Patients with general symptoms (N, %)	1166	19.9%	2801	47.8%
Incidence rate per 100 person-years	84.7		45.5	
Inpatient admission or ED visit within 14 days of event (N, %)	411	35.3%	965	34.5%
GI events				
Patients without GI events in preperiod (N, %)	8228	92.6%	8228	92.6%
Patients with GI events (N, %)	209	2.5%	949	11.5%
Incidence rate per 100 person-years	9.7		7.7	
Inpatient admission or ED visit within 14 days of event (N, %)	102	48.8%	436	45.9%
GI symptoms				
Patients without GI symptoms in preperiod (N, %)	7791	87.6%	7791	87.6%
Patients with GI symptoms (N, %)	386	5.0%	1230	15.8%
Incidence rate per 100 person-years	19.1		11.0	
Inpatient admission or ED visit within 14 days of event (N, %)	103	26.7%	398	32.4%
GI upset				
Patients without GI upset in preperiod (N, %)	5290	59.5%	5290	59.5%
Patients with GI upset (N, %)	935	17.7%	2022	38.2%
Incidence rate per 100 person-years	77.1		33.4	
Inpatient admission or ED visit within 14 days of event (N, %)	224	24.0%	673	33.3%
Hematological effects				
Patients without hematological effects in preperiod (N, %)	8456	95.1%	8456	95.1%
Patients with hematological effects (N, %)	278	3.3%	785	9.3%
Incidence rate per 100 person-years	12.5		6.2	
Inpatient admission or ED visit within 14 days of event (N, %)	130	46.8%	395	50.3%

(continued >)

nab-paclitaxel was frequently discontinued. Regimen augmentation/switch was observed in 14.1% of women; the remaining 8.7% ended their Index LOT due to the end of follow-up (Table 2). Overall, 83.1% of women had evidence of early discontinuation of the Index LOT, defined as <18 weeks (6 cycles) of therapy.

Among the 6943 patients eligible for the dose-change analysis, 3497 (50.4%) evidenced ≥ 1 IV paclitaxel/nab-paclitaxel dose change $\geq 10\%$ over the Index LOT (Table 2). Patients had a mean of 2.0 (± 1.8) dose changes; time from index to the first dose change was a mean of 39 (± 38) days. A total of 2945 patients (42.4%) had at least 1 dose reduction $\geq 10\%$, with a mean of 1.5 (± 1.0) reductions per patient. Time to the first dose reduction was a mean of 46 (± 42) days, and the mean reduced dose was 70% ($\pm 20\%$) of the prior dose. Of the 2945 patients with a dose reduction during the Index LOT, 1626 (55.2%) evidenced a dose reduction in the 14 days following a toxicity; the most common toxicities prior to dose reduction were GI upset (18.6%), myelotoxicity (14.7%), CIPN (12.6%), and neutropenia (12.1%; Table 2).

Incident Comorbidities and Toxicities

Over the full follow-up period, the most common incident comorbidities were depression (12.3%), liver dysfunction (10.5%), nonrheumatoid arthritis (8.9%), and insomnia (7.4%); incident diabetes, falls, fractures, and rheumatoid arthritis each were observed in less than 5% of the eligible women.

Toxicities were common; 95.4% of women had ≥ 1 prevalent toxicity, with a mean of 5.2 (± 3.2) toxicities over the full follow-up (Supplemental Table 1). The most common toxicities were infection (62.3%), general symptoms (53.8%), CIPN (51.6%), GI upset (50.0%), and myelotoxicity (43.3%). During the Index LOT, 78.6% of patients had claims for ≥ 1 prevalent toxicity, with a mean of 2.3 (± 2.1) toxicities. The most common toxicities during the Index LOT included GI upset (30.5%), myelotoxicity (27.0%), infection (26.2%), general symptoms (25.9%), and CIPN (22.7%).

Incident toxicities were assessed among the subset of women with no evidence of the toxicity of interest in the preperiod (Table 3). Over the full follow-up, the incidence rate of toxicities ranged from 0.2 cases/100 person-years for alopecia to 56.5 cases/100 person-years for infections. Other common incident toxicities included CIPN, general symptoms, and GI upset with 49.7, 45.5, and 33.4 cases/100 person-years, respectively. Using the presence of hospitalizations or ED visits in the 14 days following the toxicity as a proxy for severity, the most severe toxicities were neurological, renal, and pulmonary events, with 91.4%, 68.2%, and 59.9% of patients, respectively, with a hospitalization/ED visit in the 14 days following the incident toxicity. During the Index LOT, the incidence of toxicities ranged from 0.4 cases/100 person-years for alopecia to 84.7 cases/100 person-years for general symptoms. Common toxicities included CIPN, infection, and GI upset, with 79.4, 79.6, and 77.1 cases/100 person-years, respectively. Neurological, renal, and pulmonary toxicities remained the most severe with 90.2%, 65.7%, and 59.0% of patients,

TABLE 3. (continued) Incident Toxicities Among Women With mBC Who Initiated Treatment With IV Paclitaxel or IV nab-Paclitaxel

	Index LOT IV paclitaxel/nab-paclitaxel N = 8890		Full follow-up IV paclitaxel/nab-paclitaxel N = 8890	
	N/Rate	%	N/Rate	%
Infection				
Patients without infection in preperiod (N, %)	4381	49.3%	4381	49.3%
Patients with infection (N, %)	826	18.9%	2316	52.9%
Incidence rate per 100 person-years	79.6		56.5	
Inpatient admission or ED visit within 14 days of event (N, %)	300	36.3%	710	30.7%
Infusion-related/hypersensitivity effects				
Patients without infusion-related/hypersensitivity effects in preperiod (N, %)	8093	91.0%	8093	91.0%
Patients with infusion-related/hypersensitivity effects (N, %)	503	6.2%	1574	19.4%
Incidence rate per 100 person-years	24.0		14.4	
Inpatient admission or ED visit within 14 days of event (N, %)	124	24.7%	416	26.4%
Joint/muscle effects				
Patients without joint/muscle effects in preperiod (N, %)	6943	78.1%	6943	78.1%
Patients with joint/muscle effects (N, %)	431	6.2%	2085	30.0%
Incidence rate per 100 person-years	24.1		25.2	
Inpatient admission or ED visit within 14 days of event (N, %)	74	17.2%	280	13.4%
Musculoskeletal effects				
Patients without musculoskeletal effects in preperiod (N, %)	7077	79.6%	7077	79.6%
Patients with musculoskeletal effects (N, %)	251	3.6%	1322	18.7%
Incidence rate per 100 person-years	13.7		13.5	
Inpatient admission or ED visit within 14 days of event (N, %)	66	26.3%	273	20.7%
Myelotoxicity				
Patients without myelotoxicity in preperiod (N, %)	6730	75.7%	6730	75.7%
Patients with myelotoxicity (N, %)	1159	17.2%	2262	33.6%
Incidence rate per 100 person-years	73.3		27.6	
Inpatient admission or ED visit within 14 days of event (N, %)	271	23.4%	702	31.0%
Nervous system effects				
Patients without nervous system effects in preperiod (N, %)	8015	90.2%	8015	90.2%
Patients with nervous system effects (N, %)	334	4.2%	1341	16.7%
Incidence rate per 100 person-years	16.0		11.8	
Inpatient admission or ED visit within 14 days of event (N, %)	160	47.9%	584	43.5%
Encephalopathy				
Patients without encephalopathy in preperiod (N, %)	8850	99.6%	8850	99.6%
Patients with encephalopathy (N, %)	41	0.5%	185	2.1%
Incidence rate per 100 person-years	1.7		1.3	
Inpatient admission or ED visit within 14 days of event (N, %)	37	90.2%	169	91.4%
Neutropenia				
Patients without neutropenia in preperiod (N, %)	6609	74.3%	6609	74.3%
Patients with neutropenia (N, %)	804	12.2%	1394	21.1%
Incidence rate per 100 person-years	49.0		16.3	
Inpatient admission or ED visit within 14 days of event (N, %)	151	18.8%	340	24.4%
Paresthesias				
Patients without paresthesias in preperiod (N, %)	8464	95.2%	8464	95.2%
Patients with paresthesias (N, %)	212	2.5%	798	9.4%
Incidence rate per 100 person-years	9.4		6.4	
Inpatient admission or ED visit within 14 days of event (N, %)	36	17.0%	139	17.4%

(continued >)

respectively, with a hospitalization/ED visit in the 14 days following the toxicity.

All-Cause HCRU and Costs

During the full follow-up, 39.7% of patients had an inpatient admission and 43.0% had an ED visit (Table 4). Nearly all patients (99.7%) had ≥ 1 outpatient office visit with a mean of 2.0 (± 1.1) visits PPPM. All patients had ≥ 1 other outpatient service, which included claims for chemotherapy infusion, with a mean of 6.4 (± 3.8) services PPPM. In addition, 98.6% of patients used the outpatient pharmacy, with a mean of 2.9 (± 2.2) prescriptions PPPM.

Mean total all-cause costs among patients with mBC treated with IV paclitaxel/nab-paclitaxel were \$11,991 ($\pm \$11,681$) PPPM during the full follow-up period (Table 4). Inpatient costs were \$1775 ($\pm \4875) PPPM, and all-cause medical costs were \$11,274 ($\pm \$11,443$) PPPM. Other outpatient services were the primary driver of all-cause total costs at \$9067 ($\pm \9304) PPPM.

BC-related HCRU and Costs

BC-related HCRU over the full follow-up period was substantial with 7.9%, 18.1%, and 97.2% of patients with ≥ 1 inpatient admission, ED visit, and office visit, respectively (Table 4). While 100% of patients received physician-administered BC-related medications with a mean of 1.0 (± 0.8) administrations per month, 98.5% had additional BC-related other outpatient services with a mean of 4.3 (± 3.1) services per month. Approximately half of women (49.9%) filled an outpatient prescription for a BC-related medication, and 89.3% of patients filled an outpatient prescription for a medication to treat neuropathy.

Total BC-related costs among patients treated with IV paclitaxel/nab-paclitaxel were \$8173 ($\pm \9140) PPPM during the full follow-up (Table 4). BC-related medical costs were \$8031 ($\pm \9085) PPPM, with \$2445 ($\pm \5768) PPPM from physician-administered BC medications, and another \$5077 ($\pm \5536) PPPM representing costs of other outpatient services.

Discussion

In this study of 8890 women with mBC initiating IV paclitaxel or IV nab-paclitaxel, early discontinuation, dose reductions, and toxicities were common over the Index LOT. Early discontinuation occurred in 83.1% of women, and 42.4% of women in the dose-change analysis had ≥ 1 IV paclitaxel/nab-paclitaxel dose reduction $\geq 10\%$. Toxicities sufficiently serious for the patients to seek medical care (in order for them to be reported in claims data) were observed in 78.6% of women during the Index LOT. Assessment of HCRU and costs over the follow-up revealed that inpatient admissions and hospitalizations were common, and costs were substantial at \$11,991 ($\pm \$11,681$) PPPM, 68.2% of which were BC-related.

Over the Index LOT, 78.6% had evidence of a prevalent toxicity; this rose to 95.4% over the full follow-up. The rate of toxicities observed in this study are in line with previously published reports citing toxicity rates of 68% to 95% in taxane users.^{14,15} We also identified high rates of incident toxicity both over the Index LOT and full follow-up; the

TABLE 3. (continued) Incident Toxicities Among Women With mBC Who Initiated Treatment With IV paclitaxel or IV nab-paclitaxel

	Index LOT IV paclitaxel/nab-paclitaxel N = 8890		Full follow-up IV paclitaxel/nab-paclitaxel N = 8890	
	N/Rate	%	N/Rate	%
Pulmonary event				
Patients without pulmonary event in preperiod (N, %)	8053	90.6%	8053	90.6%
Patients with pulmonary event (N, %)	244	3.0%	885	11.0%
Incidence rate per 100 person-years	11.8		7.2	
Inpatient admission or ED visit within 14 days of event (N, %)	144	59.0%	530	59.9%
Renal toxicity				
Patients without renal toxicity in preperiod (N, %)	8519	95.8%	8519	95.8%
Patients with renal toxicity (N, %)	134	1.6%	529	6.2%
Incidence rate per 100 person-years	6.0		4.0	
Inpatient admission or ED visit within 14 days of event (N, %)	88	65.7%	361	68.2%
Skin effects				
Patients without skin effects in preperiod (N, %)	8689	97.7%	8689	97.7%
Patients with skin effects (N, %)	141	1.6%	388	4.5%
Incidence rate per 100 person-years	6.1		2.9	
Inpatient admission or ED visit within 14 days of event (N, %)	10	7.1%	33	8.5%

CIPN, chemotherapy-induced peripheral neuropathy; CVD, cardiovascular disease; ED, emergency department; GI, gastrointestinal; IV, intravenous; LOT, line of therapy; mBC, metastatic breast cancer.

See supplementary materials for specific toxicities in each category.

*General symptoms included fever, headache, malaise/fatigue, edema, fluid retention, epistaxis, and dysgeusia/dysosmia.

most common were CIPN, general symptoms, and infections, each occurring in approximately 50% of women over the full follow-up. Although a causal relationship between toxicities and treatment changes cannot be established in claims data, the finding that 55.2% of women with a dose reduction during the Index LOT had a dose change in the 14 days following a toxicity diagnosis suggests that toxicities impacted treatment. In a chart review to examine the relationship between toxicities and dose changes, Rashid et al found that 20% of patients with a toxicity had a change to their chemotherapy regimen, which is similar to the 23.4% of women with dose reductions in this study.²⁰

Toxicities do not only impact chemotherapy but can also drive increased HCRU. Multiple studies have reported increased health care costs in patients who experience toxicities.^{14,15} This study did not specifically address relative health care costs in patients with and without toxicities; however, the presence of ED visits or inpatient admissions was assessed in the 14 days following incident toxicities. Of the 21 toxicities assessed here, ED visits or inpatient admission rates of $\geq 30\%$ were observed for 13 toxicities. Rates of ED visits or inpatient admissions surpassed 50% for incident cardiovascular disease events and symptoms; pulmonary events; and hematological, renal, and encephalopathy.

During the full follow-up, mBC patients treated with IV paclitaxel/nab-paclitaxel in this study incurred mean health care costs of \$11,991 PPPM, or approximately \$143,892 per patient annually. BC-related costs accounted for more than two-thirds (68.2%) of the monthly all-cause costs at \$8173 PPPM or \$98,076 per patient per year. For both

all-cause and BC-related costs, other outpatient services and physician administration of BC-related medications were the primary cost drivers. Similarly, Hurvitz et al and Hansen et al examined total health care costs for mBC patients during paclitaxel treatment; they found costs ranging from approximately \$7500 to \$13,000 PPPM depending on LOT and toxicity burden.^{14,15} Other studies have also assessed the burden of mBC in broader populations (eg, not only taxane treatment) and found costs ranging from approximately \$9000 to \$11,000 PPPM, which are largely in line with this analysis.^{10,12,21,22}

In aggregate, the treatment changes, discontinuation, dose reductions, toxicities, incident comorbid conditions, and high HCRU and costs incurred by patients with mBC receiving IV paclitaxel/nab-paclitaxel demonstrate a large burden for patients and the health care system.

Limitations

This descriptive study is subject to several limitations. This analysis was limited to patients with commercial or Medicare supplemental insurance and ≥ 3 months of postindex enrollment; therefore, results may not generalize to the uninsured, those with other insurance, or patients who die shortly after initiating treatment. Second, there is the potential for clinical misclassification, as patients were identified through administrative claims data, which are subject to miscoding and undercoding. This may be particularly relevant to assessment of toxicities, as less severe conditions that may not require medical intervention (eg, headache) or conditions less likely to be coded (eg, nausea) are likely underreported. It is also extremely difficult to

discern cancer severity due to the lack of staging and biomarker information in claims. Third, all dose-change analyses were estimated using paid amounts on claims. Due to this methodology, only relative changes in dose were assessed; however, changes in factors such as rebates, variability in price of generic agents, or site of medication administration could impact estimates. Finally, this study cannot identify causal relationships between IV paclitaxel/nab-paclitaxel and toxicity development.

Conclusions

Alterations in chemotherapy, including early discontinuation and dose reductions, were common among women with mBC initiating IV paclitaxel/nab-paclitaxel in this study. High rates of toxicities were also observed, and proxy measures examining the timing between toxicities and dose reductions found that 55.2% of women with a dose reduction experienced a dose reduction shortly after a toxicity diagnosis. Similarly, high rates of hospitalizations or ED visits following severe incident toxicities (eg, encephalopathy) were observed. Treatments with increased tolerability have the potential to reduce toxicity rates, improve adherence to treatment, and improve patient outcomes. Additionally, the majority of health care costs (\$11,991 PPPM or approximately \$143,892 annually per patient) in this study were derived from other outpatient services including chemotherapy administration. These findings suggest that chemotherapy and toxicities exert a substantial burden on patients and payers; medications with improved dosing schedules and tolerability could therefore have the potential to reduce the clinical and economic burden of mBC. ♦

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from IBM Watson Health. Restrictions apply to the availability of these data, which were used under license for this study.

REFERENCES

- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7-30. doi:10.3322/caac.21590
- Cancer stat facts: female breast cancer. National Cancer Institute / Surveillance, Epidemiology, and End Results Program. Accessed June 9, 2020. <https://seer.cancer.gov/statfacts/html/breast.html> <https://seer.cancer.gov/statfacts/html/breast.html>
- DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. *CA Cancer J Clin* 2019;69(6):438-451. doi:10.3322/caac.21583

4. Mariotto AB, Etzioni R, Hurlbert M, Penberthy L, Mayer M. Estimation of the number of women living with metastatic breast cancer in the United States. *Cancer Epidemiol Biomarkers Prev*. 2017;26(6):809-815. doi:10.1158/1055-9965.EPI-16-0889
5. Curtin SC. Trends in cancer and heart disease death rates among adults aged 45-64: United States, 1999-2017. *Natl Vital Stat Rep*. 2019;68(5):1-9.
6. Waks AG, Winer EP. Breast cancer treatment: a review. *JAMA*. 2019;321(3):288-300. doi:10.1001/jama.2018.19323
7. Gradishar WJ. Taxanes for the treatment of metastatic breast cancer. *Breast Cancer (Auckl)*. 2012;6:159-171. doi:10.4137/BCBCR.S8205
8. NCCN Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network (NCCN). Breast cancer, version 4.2020. Accessed x x, 2020. https://www.nccn.org/professionals/physician_gls/
9. Rowinsky EK, Chaudhry V, Cornblath DR, Donehower RC. Neurotoxicity of taxol. *J Natl Cancer Inst Monogr*. 1993(15):107-115.
10. Blumen H, Fitch K, Polkus V. Comparison of treatment costs for breast cancer, by tumor stage and type of service. *Am Health Drug Benefits*. 2016;9(1):23-32.
11. Fu AZ, Jhaveri M. Healthcare cost attributable to recently-diagnosed breast cancer in a privately-insured population in the United States. *J Med Econ*. 2012;15(4):688-694. doi:10.3111/13696998.2012.673524
12. Ray S, Bonthapally V, McMorrow D, Bonafede M, Landsman-Blumberg P. Patterns of treatment, healthcare utilization and costs by lines of therapy in metastatic breast cancer in a large insured US population. *J Comp Eff Res*. 2013;2(2):195-206. doi:10.2217/ce.13.1
13. Kruse GB, Amonkar MM, Smith G, Skonieczny DC, Stavarakas S. Analysis of costs associated with administration of intravenous single-drug therapies in metastatic breast cancer in a U.S. population. *J Manag Care Pharm*. 2008;14(9):844-857. doi:10.18553/jmcp.2008.14.9.844
14. Hansen RN, Ramsey SD, Lalla D, et al. Identification and cost of adverse events in metastatic breast cancer in taxane and capecitabine based regimens. *Springerplus*. 2014;3:259. doi:10.1186/2193-1801-3-259
15. Hurvitz S, Guerin A, Brammer M, et al. Investigation of adverse-event-related costs for patients with metastatic breast cancer in a real-world setting. *Oncologist*. 2014;19(9):901-908. doi:10.1634/theoncologist.2014-0059
16. Force RW, Pugmire BA, Culbertson VL. Comparing medical cost of care for patients with metastatic breast cancer receiving taxane therapy: claims analysis. *Am Health Drug Benefits*. 2010;3(4):276-284.
17. SEER – Medicare: selecting the appropriate comorbidity SAS macro. National Cancer Institution / Division of Cancer Control & Population Sciences. Updated May 16, 2019. Accessed December 10, 2020. <https://healthcaredelivery.cancer.gov/seermedicare/considerations/calculation.html>
18. Cho H, Mariotto AB, Mann BS, Klabunde CN, Feuer EJ. Assessing non-cancer-related health status of US cancer patients: other-cause survival and comorbidity prevalence. *Am J Epidemiol*. 2013;178(3):339-349. doi:10.1093/aje/kws580
19. Consumer Price Index details report tables. Accessed March 1, 2020. <https://www.bls.gov/cpi/home.htm>
20. Rashid N, Koh HA, Baca HC, et al. Clinical impact of chemotherapy-related adverse events in patients with metastatic breast cancer in an integrated health care system. *J Manag Care Spec Pharm*. 2015;21(10):863-871. doi:10.18553/jmcp.2015.21.10.863
21. Montero AJ, Eapen S, Gorin B, Adler P. The economic burden of metastatic breast cancer: a U.S. managed care perspective. *Breast Cancer Res Treat*. 2012;134(2):815-822. doi:10.1007/s10549-012-2097-2
22. Schwartz KL, Simon MS, Bylsma LC, et al. Clinical and economic burden associated with stage III to IV triple-negative breast cancer: a SEER-Medicare historical cohort study in elderly women in the United States. *Cancer*. 2018;124(10):2104-2114. doi:10.1002/cncr.31299

TABLE 4. All-Cause and BC-related HCRU and Costs PPPM in Women With mBC Initiating IV Paclitaxel or IV nab-Paclitaxel

	All-cause IV paclitaxel/nab-Paclitaxel N = 8890		BC-related IV paclitaxel/nab-Paclitaxel N = 8890	
	N/Mean	%/SD	N/Mean	%/SD
HCRU, PPPM				
Inpatient				
Patients with an admission (N, %)	3527	39.7%	705	7.9%
Number of inpatient admissions (mean, SD)	0.06	0.11	0.01	0.03
Outpatient				
ED visits				
Patients with an ED visit (N, %)	3821	43.0%	1605	18.1%
Number of ED visits (mean, SD)	0.08	0.23	0.03	0.17
Outpatient office visits				
Patients with an office visit (N, %)	8865	99.7%	8637	97.2%
Number of office visits (mean, SD)	2.0	1.1	1.4	1.0
Other outpatient services ^a				
Patients with another outpatient service (N, %)	8889	100.0%	8755	98.5%
Number of other outpatient services (mean, SD)	6.4	3.8	4.3	3.1
Physician-administered BC-related medications ^b				
Patients with an administration (N, %)	–	–	8890	100.0%
Number of administrations (mean, SD)	–	–	1.0	0.8
Outpatient pharmacy				
Patients with a prescription (N, %)				
Number of prescriptions (mean, SD)	2.9	2.2	–	–
BC-related medications ^b				
Patients with a prescription (N, %)	–	–	4432	49.9%
Number of prescriptions (mean, SD)	–	–	0.2	0.3
Neuropathy treatment-related medications ^c				
Patients with a prescription (N, %)	–	–	7939	89.3%
Number of prescriptions (mean, SD)	–	–	0.7	0.8
Health care costs, PPPM^d				
Total costs (total medical + outpatient pharmacy) (mean, SD)	\$11,991	\$11,681	\$8173	\$9,140
Total medical costs (inpatient + outpatient) (mean, SD)	\$11,274	\$11,443	\$8031	\$9085
Inpatient costs (mean, SD)	\$1775	\$4875	\$244	\$1575
Outpatient costs (mean, SD)	\$9499	\$9536	\$7787	\$8870
ED visit costs (mean, SD)	\$135	\$1488	\$50	\$652
Outpatient office visit costs (mean, SD)	\$297	\$296	\$215	\$231
Other outpatient services costs (mean, SD) ^b	\$9067	\$9304	\$5077	\$5536
Physician-administered BC-related medications (mean, SD) ^b	–	–	\$2445	\$5768
Outpatient pharmacy costs (mean, SD)	\$717	\$1651	–	–
BC-related medications (mean, SD) ^b	–	–	\$94	\$381
Neuropathy treatment-related medications (mean, SD) ^c	–	–	\$48	\$432

BC, breast cancer; ED, emergency department; HCRU, health care resource utilization; PPPM, per patient per month. Mean duration of follow-up: 18.9 (±13.5) months.

^aAll-cause other outpatient services include cost of physician-administered medications.

^bBC-related medications included cytotoxic chemotherapy agents, endocrine therapy, and HER2-directed therapy.

^cNeuropathy treatment-related medications included antidepressants, anticonvulsants, opioids and narcotics, systemic corticosteroids, nonopioid and nonsteroidal pain relief drugs, topical local anesthetics, mexiletine, tocainide, and pentoxifylline.

^dHealth care costs were adjusted to 2019 costs using the medical component of the Consumer Price Index.

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