Comparison of medical costs and healthcare resource utilization of post-menopausal women with HR+/HER2− metastatic breast cancer receiving everolimus-based therapy or chemotherapy: a retrospective claims database analysis

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Original article

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Abstract

Objective:

To analyze medical costs and healthcare resource utilization (HRU) associated with everolimus-based therapy or chemotherapy among post-menopausal women with hormone-receptor-positive, human-epidermal-growth-factor-receptor-2-negative (HR+/HER2−) metastatic breast cancer (mBC).

Methods:

Patients with HR+/HER2− mBC who discontinued a non-steroidal aromatase inhibitor and began a new line of treatment with everolimus-based therapy or chemotherapy (index therapy/index date) between July 20, 2012 and April 30, 2014 were identified from two large claims databases. All-cause, BC-related, and adverse event (AE)-related medical costs (in 2014 USD) and all-cause HRU per patient per month (PPPM) were analyzed for both treatment groups across patients' first four lines of therapies for mBC. Adjusted differences in costs and HRU between the everolimus and chemotherapy treatment group were estimated pooling all lines and using multivariable generalized linear models, accounting for difference in patient characteristics.

Results:

A total of 3298 patients were included: 902 everolimus-treated patients and 2636 chemotherapy-treated patients. Compared to chemotherapy, everolimus was associated with significantly lower all-cause (adjusted mean difference = $3455, $p < 0.01$) and BC-related ($2510, $p < 0.01$) total medical costs, with inpatient ($1344, $p < 0.01$) and outpatient costs ($1048, $p < 0.01$) as the main drivers for cost differences. Everolimus was also associated with significantly lower AE-related medical costs ($1730, $p < 0.01$), as well as significantly lower HRU (emergency room incidence rate ratio [IRR] = 0.83; inpatient IRR = 0.74; inpatient days IRR = 0.65; outpatient IRR = 0.71; BC-related outpatient IRR = 0.57; all $p < 0.01$).

Conclusions:

This retrospective claims database analysis of commercially-insured patients with HR+/HER2− mBC in the US showed that everolimus was associated with substantial all-cause, BC-related, and AE-related medical cost savings and less utilization of healthcare resources relative to chemotherapy.

Introduction

Breast cancer (BC) is the most common malignancy among women worldwide, accounting for 25% of all cancers, and is the second leading cause of cancer-related death for women in developed countries[1]. It is estimated that, in 2015, ~232,000 new BC cases will be diagnosed and that BC-related deaths will account for 6.8% of all cancer-related deaths in the US[2]. BC-related deaths are primarily due to the development of incurable metastatic disease[3]. Approximately 5–10% of BC is metastatic (mBC) at the time of diagnosis[4], and 20–50% of patients who are first diagnosed with primary BC ultimately develop metastatic disease[3]. The 5-year survival rates for patients with mBC are estimated to be 20–25%[4,5]. Furthermore, mBC is associated with substantial economic burden. Studies have reported average medical costs of ~$10,000 per month per patient[6,7], with medical services comprising about half of the total healthcare costs among patients with mBC receiving chemotherapy in the US[8].

As mBC is not curable, treatment aims to prolong survival by controlling tumor growth and to improve quality-of-life (QoL) for patients[9]. The preferred mBC treatments depend on the molecular sub-type of the patient's neoplasm. The most prevalent molecular sub-type of BC is hormone-receptor-positive (HR+) human epidermal growth factor receptor-2-negative (HER2−), which comprises ~70% of mBC diagnoses[10]. HR+ disease is particularly common among post-menopausal women, as the relative incidence of HR positivity increases with age[11]. The National Comprehensive Cancer Network (NCCN) treatment guidelines recommend the use of endocrine therapy as preferred first-line treatment for post-menopausal women with HR+/HER2− mBC[4,12]. For patients who do not respond or develop resistance to the initial endocrine agent, NCCN guidelines recommend either additional endocrine therapy or chemotherapy, depending on the aggressiveness of the cancer[12]. Chemotherapy is typically used for patients with rapidly progressive or symptomatic visceral disease[8]. The targeted therapy everolimus, an inhibitor of mammalian target of rapamycin used in combination with exemestane, has also become a common treatment option for patients who previously failed a non-steroidal aromatase inhibitor (NSAI)[13].

Since the approval of everolimus for HR+/HER2− mBC in 2012, several economic modelling studies have assessed the budget impact of everolimus for payers and cost-effectiveness of everolimus compared to endocrine therapy and chemotherapy. Budget impact models suggest that everolimus use is associated with medical cost savings for the treatment of HR+/HER2− mBC, which partially offset the increased pharmacy costs and result in modest total budget increase to the payers[14,15]. Cost-effectiveness models suggest that everolimus/exemestane combination therapy is a cost-effective option compared to other endocrine therapies benchmarked by the economic value of other novel cancer medications[16] and dominate chemotherapies including bevacizumab/capecitabine and bevacizumab/paclitaxel combination therapies[17]. Cost modeling results also suggest that costs for managing adverse events (AEs) are 33–50% less for everolimus/exemestane combination therapy as compared to commonly-used single-agent chemotherapy including capecitabine, docetaxel, and doxorubicin[18]. However, no studies have yet directly assessed the economic outcomes associated with everolimus-based therapy among post-menopausal women with HR+/HER2− mBC in a real-world setting.

This study aims to fill the gap in the literature by retrospectively comparing medical costs and healthcare resource utilization for patients using everolimus-based therapy vs chemotherapy, and estimating the differences in these real-world economic outcomes. To that end, this retrospective claims database analysis compared all-cause, BC-related, and AE-related medical costs and healthcare resource utilization among patients with HR+/HER2− mBC who received everolimus-based therapy vs chemotherapy.

Methods

Data source

This study was conducted using combined administrative claims data from the Truven Health Analytics MarketScan Commercial and Medicare Supplemental (MarketScan) and IMS Health PharMetrics Plus (PharMetrics) databases spanning from January 1, 2002 to June 30, 2014. The MarketScan database captures the healthcare claims of ~40 million annually covered lives insured by employer-sponsored private health plans from over 130 employers, as well as Medicare-eligible retirees with employer-provided Medicare supplemental plans. The PharMetrics database contains combined data from over 100 healthcare plans, representing over 42 million annually covered lives insured by private health plans, Medicare Advantage, and Medicare supplemental plans. These data are nationally representative and capture information on patient demographics, diagnoses, healthcare visits, clinical expenditures including detailed costs, and healthcare utilization data for healthcare services performed in inpatient and outpatient settings, and health insurance enrollment. The medical claims are linked to prescription drug claims and person-level health insurance enrollment data. The data were de-identified and comply with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act.

Research design

A retrospective US claims database analysis was conducted to compare medical costs and healthcare resource utilization among post-menopausal women with HR+/HER2− mBC treated with everolimus-based therapy vs chemotherapy.

Sample selection and construction

Post-menopausal women with HR+/HER2− mBC who previously received a NSAI and initiated a new line of therapy for mBC were identified in the claims databases using an algorithm adapted from previous studies[19,20]. Selected patients were required to have: (1) at least two diagnoses for BC (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code: 174.xx) on distinct medical claims, separated by at least 30 days; and (2) diagnoses for a secondary neoplasm (ICD-9-CM codes: 196.xx–197.xx, 198.0, 198.1, 198.3–198.7, 198.81, 198.89) on at least two medical claims, (1) no more than 30 days before, or (2) any time after the first BC diagnosis. Patients with HR+ BC were identified by at least one prescription fill for an endocrine therapy at any time, and patients with HER2− disease were identified as lacking any prescriptions for the treatment of HER2+ disease (trastuzumab, lapatinib, pertuzumab, or ado-trastuzumab). Patients were considered post-menopausal if they fulfilled any of the following criteria: (1) were at least 60 years old at mBC diagnosis; (2) had a prescription fill or medical claim for an aromatase inhibitor or fulvestrant; (3) had a prior bilateral oophorectomy; or (4) had at least one diagnosis related to post-menopausal status or menopause (e.g., unspecified menopausal and post-menopausal disorders: ICD-9-CM code 627.9).

Among post-menopausal women with HR+/HER2− mBC, patients with at least one eligible line of therapy among their first four lines of treatment for mBC were included in the analysis. Eligible lines of therapy must have been initiated between July 20, 2012 (the FDA approval date of everolimus for HR+/HER2− mBC) and March 31, 2014 (to ensure at least 3 months of potential follow-up). Patients must have received an NSAI prior to the date of initiation of index therapy; the beginning of the line of therapy was defined as index date. Additionally, patients were required to have at least 12 months of continuous health plan enrollment prior to (for studying patients' baseline characteristics) and at least 4 weeks of continuous enrollment following the index date (to exclude patients with very short follow-up, among whom the costs and healthcare resource utilization information might not be complete).

Patient's eligible line(s) of therapies were numbered chronologically from the date of mBC diagnosis up to the first four lines and classified into mutually exclusive regimen groups (everolimus-based therapy and chemotherapy). Each line of therapy started at the index date and ended at a treatment change (switch or add-on), a discontinuation, the end of insurance eligibility, or the end of data availability (June 30, 2014), whichever occurred first. Treatment discontinuation was defined as a treatment gap of at least 60 days. Everolimus-based therapy included everolimus monotherapy or a combination of everolimus with another therapy for mBC. Chemotherapy included chemotherapy monotherapy, combination therapy of chemotherapy agents, and combination therapy of chemotherapy and endocrine therapy.

Study variables

Patient baseline characteristics

Patients' baseline characteristics were assessed at the beginning of each line of therapy, during the 12 months preceding the index date. Patient characteristics included health insurance plan type, mBC disease status (de novo, non-de novo, or type unknown), number of organ-level metastatic sites, Charlson Comorbidity Index (CCI)[21], prior use of chemotherapy for mBC, and time from initiation of last adjuvant endocrine therapy to first mBC diagnosis.

Cost and healthcare resource utilization

Cost outcomes analyzed in this study included all-cause, BC-related, and AE-related medical costs associated with inpatient, outpatient, emergency room (ER), and other medical services. Costs were measured from a combined payer and patient out-of-pocket cost perspective. The cost variables used in the study included the amount paid by the health plan, as well as the deductible, co-payment, co-insurance, and co-ordination of benefits amounts (where for Medicare Supplemental enrolled patients, it includes the portion reimbursed by Medicare). All-cause medical costs were defined as costs incurred by any medical services during the studied line of therapy. BC-related medical costs were assessed as costs incurred by medical services that were associated with a diagnosis of BC (ICD-9-CM code 174.xx) or a secondary neoplasm (ICD-9CM codes 196.xx–197.xx, 198.0, 198.1, 198.3–198.7, 198.81, or 198.89). AE-related medical costs were defined as costs of medical services that were associated with a diagnosis for an AE (Supplemental Table 1)[22]. Costs were inflated to 2014 US dollars using the medical care component of the Consumer Price Index (CPI) and reported on a per patient per month (PPPM) basis to account for varying duration across lines of therapies.

Healthcare resource utilization outcomes analyzed in this study included number of emergency care visits (defined as inpatient hospitalizations and emergency

Table 1. Baseline characteristics.

	Line 1		Line 2		Line 3		Line 4	
	Everolimus (n = 66)	Chemotherapy (n = 553)	Everolimus (n = 261)	Chemotherapy (n = 823)	Everolimus (n = 331)	Chemotherapy (n = 1004)	Everolimus (n = 282)	Chemotherapy (n = 1030)
Descriptive characteristics								
Age at index date (years), mean ±SD [median]	62.8 ± 9.0 [62.7]	62.4 ± 10.3 [61.0]	60.9 ± 9.7 [60.4]	60.9 ± 10.2 [60.1]	59.5 ± 10.4 [59.8]	60.3 ± 9.8 [59.9]	60.7 ± 10.7 [60.9]	59.4 ± 10.1 [58.9]*
Insurance type, n (%)								
Medicare	19 (28.8%)	195 (35.3%)	59 (22.6%)	234 (28.4%)	82 (24.8%)	269 (26.8%)	80 (28.4%)	241 (23.4%)
Medicare advantage	3 (4.5%)	5 (0.9%)*	5 (1.9%)	9 (1.1%)	0 (0.0%)	14 (1.4%)*	1 (0.4%)	7 (0.7%)
Medicare supplemental	12 (18.2%)	148 (26.8%)	41 (15.7%)	174 (21.1%)	66 (19.9%)	195 (19.4%)	63 (22.3%)	181 (17.6%)
Other medicare	4 (6.1%)	42 (7.6%)	13 (5.0%)	51 (6.2%)	16 (4.8%)	60 (6.0%)	16 (5.7%)	53 (5.1%)
Private insurance only	47 (71.2%)	358 (64.7%)	202 (77.4%)	589 (71.6%)	249 (75.2%)	735 (73.2%)	202 (71.6%)	789 (76.6%)
mBC characteristics,[a] n (%)								
De novo	3 (4.5%)	33 (6.0%)	67 (25.7%)	204 (24.8%)	116 (35.0%)	283 (28.2%)*	70 (24.8%)	326 (31.7%)*
Non-de novo	62 (93.9%)	520 (94.0%)	169 (64.8%)	581 (70.6%)	166 (50.2%)	593 (59.1%)**	140 (49.6%)	524 (50.9%)
Type of mBC unknown	1 (1.5%)	0 (0.0%)	25 (9.6%)	38 (4.6%)**	49 (14.8%)	128 (12.7%)	72 (25.5%)	180 (17.5%)**
Number of organ-level metastatic sites, mean ±SD [median]	1.3 ± 1.0 [1]	1.4 ± 1.1 [1]	1.7 ± 1.1 [1]	1.8 ± 1.3 [2]	1.9 ± 1.2 [2]	2.0 ± 1.4 [2]	2.0 ± 1.3 [2]	2.1 ± 1.4 [2]
CCI, mean ±SD [median]	9.5 ± 1.7 [9]	9.0 ± 1.2 [9]	8.8 ± 1.0 [9]	9.1 ± 1.3 [9]***	8.8 ± 1.0 [9]	9.1 ± 1.2 [9]***	8.9 ± 1.0 [9]	9.0 ± 1.1 [9]
Prior use of chemotherapy for mBC, n (%)	0 (0.0%)	0 (0.0%)	28 (10.7%)	305 (37.1%)***	105 (31.7%)	602 (60.0%)***	162 (57.4%)	777 (75.4%)***
Time from initiation of last adjuvant endocrine therapy to mBC diagnosis (months), mean ±SD [median]	18.9 ± 20.8 [12.2]	28.9 ± 26.5 [21.3]**	23.7 ± 22.7 [16.7]	22.6 ± 23.3 [14.5]	20.6 ± 22.0 [10.7]	22.0 ± 22.0 [15.1]	15.9 ± 18.1 [10.0]	17.6 ± 18.4 [11.9]

SD, standard deviation; CCI, Charlson comorbidity index; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a]De novo patients are defined as being diagnosed for mBC within 3 months of their first diagnosis for BC; non-de novo patients are defined as patients whose mBC diagnosis date is at least 3 months after their first diagnosis. Both de novo and non-de novo patients are required to have at least 12 months of continuous eligibility prior to the BC diagnosis date; otherwise, they are considered to have unknown mBC type.

room [ER] visits), inpatient hospitalizations, days of inpatient hospitalization, ER visits, outpatient visits, BC-related outpatient visits (defined as the use of outpatient services associated with a diagnosis of BC or a secondary neoplasm), and other medical services visits (e.g., laboratory, home care, and hospice services) occurring during the studied line of therapy. AE-related utilization was additionally summarized as services that were associated with a diagnosis for an AE (Supplementary Table 1)[22]. Healthcare resource utilization outcomes were calculated on a PPPM basis.

Statistical analysis

Patient baseline results were compared between everolimus and chemotherapy using Wilcoxon rank-sum tests for continuous variables and Chi-square tests for categorical variables.

Unadjusted costs were compared between everolimus and chemotherapy by line of therapy using Wilcoxon rank-sum tests. Adjusted cost differences were estimated across all lines using multivariable two-part models, where the first part was a logistic regression model and the second part a gamma generalized linear model (GLM). P-values were estimated using a non-parametric bootstrap re-sampling technique with 499 iterations. Multivariable models adjusted for differences in patient baseline characteristics, including health insurance plan type (private insurance only, Medicare Advantage, Medicare Supplemental, and other Medicare coverage), disease status (de novo, non-de novo, and type unknown), number of metastatic sites, CCI, prior use of chemotherapy for mBC, and time from initiation of last adjuvant endocrine therapy to mBC.

Unadjusted and adjusted healthcare resource utilization was compared between everolimus and chemotherapy by line of therapy (unadjusted) and across all eligible lines (adjusted) using GLMs with a log link and Poisson distribution. Results were reported as incidence rate ratios (IRRs). P-values were estimated using the bootstrapping technique discussed above. Multivariable models were adjusted for differences in patient baseline characteristics listed above for cost multivariable models.

Results

A total of 3298 patients who used everolimus-based therapy or chemotherapy as their index treatment in the first four lines of therapy for mBC were selected. A total of 62.6% were from the MarketScan database and 37.4% were from the PharMetrics database. One patient could contribute more than one line of the same type of therapy (e.g., two lines of chemotherapy) or different types of therapy (e.g., one line of chemotherapy and one line of everolimus-based therapy). The sample included 902 patients who contributed to 940 lines of everolimus-based therapy and 2636 patients who contributed to 3410 lines of chemotherapy (Figure 1). Among these patients, 240 patients contributed to both everolimus-based therapy and chemotherapy. Baseline characteristics are summarized in Table 1.

Across the first four lines of therapy, patients treated with everolimus and chemotherapy had generally similar characteristics. Patients were ∼60 years old and had similar mBC disease status, number of metastatic sites, and CCI across all lines. However, a lower proportion of patients treated with everolimus previously received chemotherapy for mBC (Line 2: 10.7% vs 37.1%; Line 3: 31.7% vs 60.0%; Line 4: 57.4% vs 75.4%, respectively; all $p < 0.001$; Table 1) compared to patients treated with chemotherapy. In addition, in Line 1, patients treated with everolimus had a significantly shorter time from initiation of last adjuvant endocrine therapy to the first mBC diagnosis compared with patients treated with chemotherapy (18.9 vs 28.9 months, $p < 0.01$; Table 1). Across all lines of therapy, 31.1% of patients treated with everolimus and 47.3% of patients treated with chemotherapy had less than 3 months of follow-up.

Across the first four lines of therapy, total unadjusted PPPM all-cause medical service costs (Table 2) were lower for patients treated with everolimus than those treated with chemotherapy. All-cause medical costs ranged from $4790–$6158 for patients treated with everolimus and $8493–$8889 for patients treated with chemotherapy. Cost differences were between $2335–$3980 PPPM and were significantly different for all lines of therapy ($p < 0.05$). Patients treated with everolimus also had significantly lower costs associated with outpatient visits across all four lines of therapy than patients treated with chemotherapy (cost differences ranging from $967–$1699 PPPM, all $p < 0.01$; Table 2).

Patients treated with everolimus also had lower PPPM BC-related medical service costs (Table 2) compared with patients treated with chemotherapy. Across lines of therapy, patients treated with everolimus incurred BC-related medical costs ranging from $3355–$5155, while those treated with chemotherapy incurred costs ranging from $6090–$6929. Cost differences were significant (all $p < 0.01$) in lines 2–4 and ranged from $1692–$3574. Patients treated with everolimus also had significantly lower costs associated with BC-related outpatient visits across lines 2–4 than patients treated with chemotherapy (cost differences were $614, $737, and $1376 for lines 2–4, respectively; all $p < 0.01$; Table 2).

Similar results were observed after pooling all lines and adjusting for patient baseline characteristics (Table 2). Everolimus was associated with significantly lower PPPM all-cause medical service costs than chemotherapy (adjusted mean difference = $3455, $p < 0.01$), with inpatient costs (difference = $1897, $p < 0.01$) and outpatient

Metastatic breast cancer (mBC): Patients with ≥2 claims for BC (ICD-9-CM: 174.xx) at least 30 days apart and ≥2 claims for secondary neoplasm on different days
(n = 179,093)

HR+/HER2-mBC: Patients with ≥1 prescription fill for (or administration of) an ET at any time and no claims for trastuzumab, lapatinib, pertuzumab, or ado-trastuzumab
(n = 98,386)

Post-menopausal females: Female patients ≥60 years old at mBC diagnosis or who had (1) aclaim for an aromatase inhibitor or fulvestrant, (2) a procedure code for bilateral oophorectomy, or (3) other procedure code related to post-menopausal status
(n = 86,137)

Index date: Patients who initiated a new line of therapy (i.e., index therapy) onor after July 20, 2012 and prior to March 31, 2014
(n = 21,141)

Treatment history: Patients who received non-steroidal aromatase inhibitor at any time prior to the index date (i.e., date of initiation of new line of therapy) and who had ≥12 months of continuous eligibility prior to index date and ≥4 weeks of continuous eligibility after the index date
(n = 8,554)

Study cohorts: Patients who initiated everolimus-based therapy or chemotherapy as their index therapy
(n= 3,298)

Everolimus-based therapy
(n = 902 for
940 total lines*)
Line 1 (n = 66)
Line 2 (n = 261)
Line 3 (n = 331)
Line 4 (n = 282)

Chemotherapy
(n = 2,636 for
3,410 total lines*)
Line 1 (n = 553)
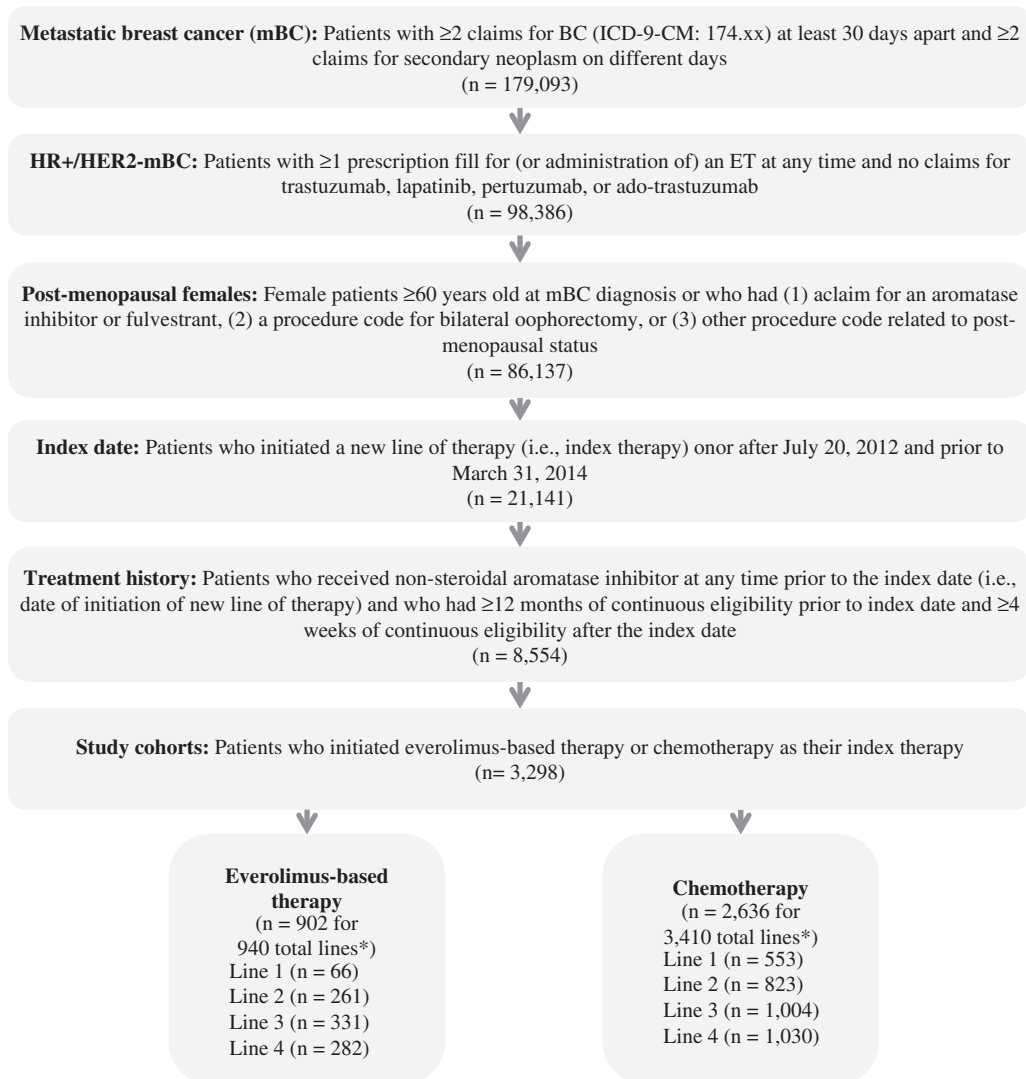Line 2 (n = 823)
Line 3 (n = 1,004)
Line 4 (n = 1,030)

Figure 1. Sample selection. *Total lines of therapy may exceed the number of patients if patients receive more than one line of the same therapy type.

costs (difference = $1395, $p < 0.01$) as the main drivers for differences in all-cause medical costs. The same trend was seen in PPPM BC-related medical service costs (difference = $2510, $p < 0.01$). Inpatient (difference = $1344, $p < 0.01$) and outpatient (difference = $1048, $p < 0.01$) cost differences were the main drivers of differences in BC-related medical costs as well. There was a lack of differences in either all-cause or BC-related ER costs between everolimus and chemotherapy.

Significant differences in PPPM AE-related medical service costs (Table 2) were also observed in lines 2–4 when comparing everolimus and chemotherapy. Patients treated with everolimus had lower PPPM costs (ranging from $1474–$1637) than patients treated with chemotherapy (ranging from $2882–$3741). Cost differences ranged from $1370–$2233 (all $p < 0.01$). Adjusted results pooling all lines and adjusting for baseline characteristics

confirmed this finding. Everolimus was associated with significantly lower PPPM AE-related medical service costs, with cost difference of $1730 ($p < 0.01$; Table 2).

Consistent with the results of the cost analysis, patients treated with everolimus used significantly fewer healthcare resources (Table 3) than patients treated with chemotherapy, in terms of numbers and days of inpatient hospitalizations (lines 1, 2, and 4), outpatient visits and BC-related outpatient visits (all lines), and other medical services (such as laboratory tests; lines 1, 2, and 4). Patients treated with everolimus were also associated with lower AE-related healthcare resource utilization, including inpatient admissions (lines 1, 2, and 4), outpatient (all lines), and other medical services related to AEs (lines 3 and 4).

After pooling all lines and adjusting for baseline characteristics (Table 3), patients treated with everolimus had significantly fewer emergency care visits (IRR = 0.83;

Table 2. Comparison of medical services costs[a] between everolimus and chemotherapy.

Costs (in 2014 $), mean ± SD	Line 1			Line 2			Line 3			Line 4			Pooled (lines 1–4)
	Everolimus (n = 66)	Chemotherapy (n = 553)	Unadjusted difference	Everolimus (n = 261)	Chemotherapy (n = 823)	Unadjusted difference	Everolimus (n = 331)	Chemotherapy (n = 1004)	Unadjusted difference	Everolimus (n = 282)	Chemotherapy (n = 1030)	Unadjusted difference	Adjusted difference
Total all-cause medical service costs	5191 ± 5696	8889 ± 14344	3698*	5023 ± 7905	8885 ± 20551	3862***	6158 ± 18987	8493 ± 38625	2335***	4790 ± 11276	8770 ± 19118	3980***	3455***
Inpatient costs	1814 ± 4761	3700 ± 12083	1886	1746 ± 6512	4335 ± 19932	2589	2833 ± 18450	4156 ± 38007	1323	1580 ± 10004	3907 ± 16840	2327	1897**
Emergency room costs	161 ± 635	193 ± 846	33	74 ± 263	139 ± 956	65	105 ± 328	164 ± 1211	59	136 ± 571	219 ± 1222	84	65**
Outpatient costs	3058 ± 3712	4757 ± 7664	1699**	3066 ± 4189	4200 ± 5470	1134***	3010 ± 4626	3977 ± 5215	967***	2828 ± 4213	4375 ± 6914	1547***	1395***
Other medical service costs	158 ± 450	239 ± 1012	81	138 ± 559	211 ± 1014	73	209 ± 798	195 ± 887	−14	246 ± 1287	269 ± 1052	23	27
Total BC-related medical service costs	3767 ± 4972	6446 ± 12940	2679	3993 ± 6744	6090 ± 12901	2098***	5155 ± 18570	6846 ± 37826	1692**	3355 ± 4446	6929 ± 15919	3574***	2510***
Inpatient costs	1101 ± 3699	2761 ± 10796	1660	1313 ± 5464	2737 ± 12276	1423	2480 ± 18225	3446 ± 37323	966	739 ± 2356	2861 ± 13304	2122	1344**
Emergency room costs	47 ± 157	95 ± 699	47*	39 ± 218	46 ± 305	6	52 ± 238	61 ± 483	10	40 ± 275	115 ± 1019	75	31*
Outpatient costs	2533 ± 3601	3444 ± 6881	911	2595 ± 3872	3209 ± 4483	614**	2475 ± 3810	3212 ± 4745	737***	2384 ± 3677	3760 ± 6727	1376***	1048**
Other medical service costs	85 ± 281	146 ± 927	60	45 ± 230	99 ± 420	54*	147 ± 723	127 ± 679	−20	192 ± 1170	193 ± 916	1*	26
AE-related medical service costs	1637 ± 3368	3340 ± 10549	1704	1474 ± 5791	3694 ± 18442	2220**	1509 ± 4514	3741 ± 36688	2233***	1512 ± 9832	2882 ± 9907	1370**	1730**

Difference, difference of chemotherapy group and everolimus group; SD, standard deviation; BC, breast cancer; AE, adverse event; $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.
[a]Medical service costs include costs from medical claims that are not associated with drug administration.

Table 3. Comparison of healthcare resource utilization between everolimus and chemotherapy[a].

	Line 1			Line 2			Line 3			Line 4			Pooled (lines 1–4)
	Everolimus (n = 66)	Chemotherapy (n = 553)	Unadjusted IRR	Everolimus (n = 261)	Chemotherapy (n = 823)	Unadjusted IRR	Everolimus (n = 331)	Chemotherapy (n = 1004)	Unadjusted IRR	Everolimus (n = 282)	Chemotherapy (n = 1030)	Unadjusted IRR	Adjusted IRR
Emergency care visits	0.142	0.201	0.71	0.123	0.141	0.87	0.129	0.138	0.93	0.120	0.177	0.68**	0.83**
Inpatient admissions	0.059	0.097	0.61*	0.052	0.076	0.69*	0.053	0.063	0.84	0.049	0.074	0.66***	0.74***
Inpatient days	0.347	0.729	0.48**	0.408	0.685	0.60*	0.381	0.466	0.82	0.307	0.589	0.52**	0.65**
Emergency room visits	0.083	0.104	0.79	0.071	0.065	1.09	0.076	0.075	1.01	0.071	0.103	0.69*	0.90
Outpatient visits	3.442	5.500	0.63**	3.389	4.764	0.71**	3.298	4.497	0.73**	3.207	4.715	0.68**	0.71**
BC-related outpatient visits	2.507	3.717	0.67**	2.309	3.389	0.68**	2.302	3.372	0.68**	2.225	3.658	0.61**	0.66***
Other medical services	0.466	0.915	0.51**	0.436	0.804	0.54**	0.545	0.676	0.81	0.491	0.799	0.61**	0.67***
AE-related HRU	0.760	1.635	0.46**	0.871	1.487	0.59**	0.782	1.449	0.54**	0.890	1.556	0.57**	0.59***
Inpatient admissions	0.053	0.086	0.61*	0.047	0.069	0.69*	0.046	0.055	0.84	0.042	0.065	0.64**	0.73***
Emergency room visits	0.053	0.056	0.94	0.046	0.039	1.19	0.043	0.051	0.85	0.042	0.057	0.74	0.93
Outpatient visits	0.581	1.355	0.43**	0.710	1.301	0.55**	0.635	1.224	0.52**	0.748	1.293	0.58**	0.57***
Other medical services	0.073	0.138	0.53	0.068	0.079	0.86	0.059	0.119	0.49**	0.058	0.140	0.42**	0.59***

IRR, incidence rate ratio of everolimus group to chemotherapy group; AE, adverse event; $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.
[a]The chemotherapy group was used as the reference group. An IRR <1 suggests that the everolimus group utilized less resources than the chemotherapy group, while an IRR >1 suggests that the everolimus group utilized more resources than the chemotherapy group.

potentially driven by large differences in line 4), inpatient admissions (IRR = 0.74), inpatient days (IRR = 0.65), outpatient visits (IRR = 0.71), BC-related outpatient visits (IRR = 0.66), and other medical services (IRR = 0.67) (all $p < 0.01$). Patients treated with everolimus were also associated with lower AE-related healthcare resource use (IRR = 0.59), including inpatient admissions (IRR = 0.73), outpatient visits (IRR = 0.57), and other medical services (IRR = 0.59) (all $p < 0.01$).

To the best of our knowledge, this study is the first to examine healthcare costs and resource utilization among patients receiving everolimus vs chemotherapy in a real-world setting, using two large US commercial claims databases. This study found that everolimus was associated with significantly lower all-cause and BC-related total medical costs compared to chemotherapy, with inpatient and outpatient costs as the main drivers in cost savings. In addition, everolimus was also associated with significantly lower AE-related medical costs compared to chemotherapy. Healthcare resource utilization results were consistent with costs results, showing that everolimus was associated with significantly lower use of various healthcare resources compared to chemotherapy. Furthermore, AE-related resource use was a major driver of emergency care visits, including inpatient hospitalizations and emergency room visits, both of which were lower for patients using everolimus.

The real-world results of this study support the findings of recent economic modeling studies showing a medical cost advantage of everolimus-based therapy vs chemotherapy. Xie et al.[14] conducted a budget impact analysis to estimate costs of everolimus as the first- and second-line treatment option after failure of an NSAI for post-menopausal women with HR+/HER2− mBC in the US. They found that everolimus was associated with reduced medical services costs, such as those reported in the current study. A similar study by Lewis et al.[15] modeled 5-year costs for the same population in Central Asia and reached similar conclusions about reduced medical costs of everolimus due to improvement in disease management. In addition, a recent study by Kourlaba et al.[17] applied data collected from clinical trials to a Markov model that compared the costs-effectiveness of everolimus/exemestane combination therapy vs two bevacizumab-based chemotherapy regimens, including bevacizumab/paclitaxel combination therapy and bevacizumab/capecitabine combination therapy, from a third-party payer's perspective over a lifetime horizon. The authors concluded that everolimus was associated with greater quality-adjusted life-years gained and lesser lifetime healthcare costs, suggesting that everolimus might be a dominant alternative compared to bevacizumab-based chemotherapies for the treatment of HR+/HER2− mBC after initial failure of NSAIs.

Use of chemotherapy is associated with a high incidence of severe AEs, which can increase overall treatment costs. A claims database study of women under 65 with BC found those who received chemotherapy had significantly higher rates of hospitalization and number of ER visits related to AEs compared with those who did not receive chemotherapy, and subsequently incurred considerable costs for these AEs (~$1271/patient/year)[23]. Another claims database analysis of AE-related costs for patients with mBC found that AEs related to chemotherapy increased monthly costs from 9–70%, depending on the severity of the AEs, driven primarily by inpatient, outpatient, and pharmacy costs[22]. The present study's findings that, across the first four lines for HR+/HER2− mBC, AE-related medical costs for everolimus were 40–52% of costs for chemotherapy, are also supported by a recent economic modeling study on the costs of managing severe AEs (grades 3 or 4) during treatment with everolimus vs chemotherapy in Western Europe[18]. That study reported AE-related per patient costs were 33–50% less for treatment with everolimus/exemestane combination therapy compared with single-agent chemotherapy.

The findings from this study have important implications for the decision-making process of healthcare stakeholders, particularly payers. In addition to safety and efficacy, payers must also weigh the impact a therapy may have on patient QoL, productivity, and healthcare resource utilization and costs. As the projected cost of BC is expected to hit $36.5 billion per year by 2020 in the US[24], strategies to reduce this expense while maintaining optimal outcomes for patients with BC are highly important. The present study indicates that treatment with everolimus for HR+/HER2− mBC results in lower total medical costs than chemotherapy, driven by fewer outpatient and inpatient visits, as well as lower costs related to AEs. This may be attributed to everolimus' superior effectiveness, with better overall survival, progression-free survival, and time on treatment compared with chemotherapy reported in real-world studies[25], and consequently fewer healthcare resources are required.

QoL considerations are increasingly important to patients with BC as the survival rates continue to increase and survivors are living longer[26]. The incidence and severity of AEs, which are higher during treatment with chemotherapy than with everolimus due to chemotherapy's toxicity, directly impact QoL among patients with BC[27]. A recent analysis of QoL data from the BOLERO-2 trial reported that, in contrast to chemotherapy, everolimus/exemestane combination therapy did not have a negative impact on health-related QoL[28]. Thus, the lower AE-related medical costs for everolimus, bolstered by previous models which showed lower costs and higher quality-adjusted life-year gained in patients with HR+/HER2− mBC using everolimus vs chemotherapy[29], are valuable evidence for considering mBC treatments that can maintain QoL while reducing AEs as well as costs.

This study has some limitations inherent to the use of claims databases. First, the databases used did not contain direct information for identification of post-menopausal HR+/HER2− mBC or on lines of treatment, therefore patient identification and treatment line classification relied on an algorithm which is based on a combination of different proxies. Similarly, certain clinical factors that may impact treatment decisions (e.g., patients' performance status) were not available in the database and cannot be adjusted for in multivariable models. Second, costs may vary across payer type, for example, commercial insurance, Medicare, and Medicaid. However, the current databases only include commercially-insured patients and those who have commercial insurance supplementing Medicare insurance; thus, the current results may not be generalizable across patient populations insured by other payers. Future studies using different claims databases, e.g., Medicare databases, can help provide additional real-world economic evidence between everolimus and chemotherapy. Finally, only direct medical costs were studied. Information to determine indirect costs, such as lost productivity and burden to caregivers, was not available.

Conclusion

This retrospective claims database analysis of patients with HR+/HER2− mBC in the US showed that everolimus was associated with substantial all-cause, BC-related, and AE-related medical cost savings and less utilization of healthcare resources relative to chemotherapy. In a commercially insured population, everolimus-based therapy was associated with adjusted total medical cost savings of $3455 PPPM compared to chemotherapy across lines of therapy.

Transparency

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