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ORIGINAL RESEARCH

Real-World Analysis of Medical Costs and Healthcare Resource Utilization in Elderly Women with HR+/HER2− Metastatic Breast Cancer Receiving Everolimus-Based Therapy or Chemotherapy

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ABSTRACT

Introduction: The objective of this study was to analyze medical costs and healthcare resource utilization (HRU) associated with everolimus-based therapy or chemotherapy among elderly women with hormone-receptor-positive, human-epidermal-growth-factor-receptor-2-negative (HR+/HER2−) metastatic breast cancer (mBC).

Methods: Elderly women (≥65 years) with HR+/HER2− mBC who failed a non-steroidal-aromatase-inhibitor and subsequently began a new line of treatment with everolimus-based therapy or chemotherapy for mBC (index therapy) during July 20, 2012 to March 31, 2014 were identified from two large commercial claims databases. All-cause, BC-, and adverse event (AE)-related medical costs (2014 USD), and all-cause and AE-related HRU per patient per month (PPPM) were compared between patients treated with everolimus-based therapy and chemotherapy across their first four lines of therapy for mBC. Adjusted costs and HRU differences were estimated by pooling all lines and using multivariable models adjusted for differences in patient characteristics.

Results: In total, 925 elderly patients (mean age approximately 73 years) with HR+/HER2− mBC met the inclusion criteria; 230 received everolimus-based therapy (240 lines) and 737 received chemotherapy (939 lines). Compared with chemotherapy, everolimus-based therapy was associated with significantly lower total all-cause PPPM medical services costs (adjusted mean difference: $4007), driven by lower inpatient ($1994) and outpatient ($1402) costs; lower BC-related medical services costs ($3129), driven by both BC-related inpatient

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($1883) and outpatient costs ($913); and lower AE-related medical services costs ($1873; all $P < 0.01$). Additionally, compared to patients treated with chemotherapy, patients treated with everolimus-based therapy had fewer all-cause outpatient visits (adjusted incidence rate ratio = 0.69), BC-related outpatient visits (0.66), other-medical-service visits (0.65), and AE-related HRU (0.59), which was driven by significantly fewer AE-related outpatient visits (0.56; all $P < 0.01$). Subgroup analyses comparing medical costs of everolimus-based therapy with capecitabine monotherapy showed consistent results overall.

Conclusion: This retrospective claims database analysis of elderly women with HR+/HER2− mBC in the United States showed that everolimus-based therapy was associated with significantly lower all-cause, BC-related, and AE-related medical services costs and less use of healthcare resources compared with chemotherapy.

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Keywords: Chemotherapy; Costs; Elderly; Everolimus-based therapy; Healthcare resource utilization; HR+/HER2− metastatic breast cancer; Oncology

INTRODUCTION

Breast cancer (BC) is the most common cancer among women worldwide [1] and is one of the leading cause of cancer deaths among the elderly population [2]. At the time of BC diagnosis, 5–10% of cases already present with metastases (mBC) [3] and up to 50% of patients diagnosed with primary BC will eventually develop incurable metastatic disease [4]. The incidence of BC rises with age, resulting in an incidence rate of BC among elderly women (≥65 years) over four times higher than that of younger women [5]. As overall life expectancy has significantly increased over the past decades, the proportion of elderly women within the United States (US) population and among mBC patients has also risen [6]. Currently, the median age at the time of BC diagnosis is 61 years, with over 40% of patients aged 65 years or older [7]. Elderly patients are more likely to develop BC of the hormone-receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2−) subtype compared to younger patients [8]. This is mainly explained by HR positivity increasing with age and being common among post-menopausal women [9]. Older patients are also less likely to have HER2-overexpressing BC due the declining number of growth factor receptors with age [8].

The treatment of mBC in the elderly is challenging due to an increased prevalence of comorbidities and sensitivity to cancer treatment's adverse effects (AEs) compared with younger patients [10]. For HR+/HER2− mBC, the National Comprehensive Cancer Network (NCCN) treatment guidelines recommend first-line treatment with endocrine therapy [11]. For patients who do not respond or develop resistance to first-line treatment, NCCN guidelines recommend treatment with additional endocrine therapy or chemotherapy [11]. Chemotherapy is considered for treatment of patients with rapidly progressive or symptomatic visceral disease, but its toxicity can result in a high incidence of AEs [12], which may be more difficult for elderly patients to tolerate [13].

The targeted therapy everolimus, an inhibitor of mammalian target of rapamycin, is an alternative option for patients with HR+/HER2− mBC refractory to a non-steroidal

aromatase inhibitor (NSAI) [14]. BOLERO-2 (ClinicalTrials.gov identifier, NCT00863655), a phase III randomized trial, demonstrated that adding everolimus to exemestane was associated with superior efficacy compared to exemestane alone and tolerable AEs [15]. A subgroup analysis of the BOLERO-2 trial showed that patients older than 65 years, as well as those 70 years and older, experienced greater improvements compared to younger patients in all efficacy endpoints, i.e., progression-free survival (PFS), overall response rate, and clinical benefit rate following everolimus/exemestane combination therapy [16]. In addition, the safety profile of everolimus-based therapy in elderly patients with advanced BC was mild to moderate [16, 17].

Prior studies have documented a high economic burden experienced by patients with mBC. Among women with HR+/HER2− mBC receiving chemotherapy, medical service costs have been shown to comprise approximately 50% of the total healthcare costs incurred by women of all ages and 75% of the total healthcare costs incurred by elderly women [18]. Cost-effectiveness models suggest that everolimus-based therapy could be considered a cost-effective option compared to endocrine monotherapy [19] as well as bevacizumab-based chemotherapy [20]. However, no studies have focused on elderly patients treated with everolimus-based therapy and compared their medical costs and healthcare resource utilization to those of patients treated with chemotherapy. There are few real-world studies on economic outcomes related to the treatment with everolimus-based therapy for HR+/HER2− mBC, and to date, no studies have directly addressed this among elderly patients. A recent claims-based study evaluating resource use and costs among post-menopausal women with HR+/HER2− mBC treated with everolimus-based therapy or chemotherapy found that everolimus-based therapy was associated with reduced medical costs as well as lower healthcare resource use [21]. However, studies of younger populations may not be generalizable to the elderly population, as treatment of BC in older patients requires additional considerations that may not be relevant to younger patients [7]. Therefore, the objective of this study was to compare all-cause, BC-related, and AE-related economic outcomes among elderly women with HR+/HER2− mBC who were treated with everolimus-based therapy or chemotherapy, including a subgroup of patients treated with capecitabine monotherapy, an oral chemotherapy agent commonly used in elderly patients [22–24].

METHODS

Data Source

This study was conducted using two pooled US-based commercial 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 approximately 40 million annually covered lives insured by employer-sponsored private health plans from over 130 employers, and Medicare-eligible retirees and their dependents with employer-sponsored 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 geographically representative and

capture information on patient demographics, diagnoses, health insurance enrollment, and healthcare visits and associated costs.

Patient Selection and Study Design

This retrospective study identified within the claims databases women aged 65 years and older with HR+/HER2− mBC who previously received an NSAI and initiated a new line of therapy for mBC, using an algorithm adapted from previous studies [25, 26]. 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, and 198.89) on at least two medical claims no more than 30 days before or any time after the first BC diagnosis. Patients with HR+/HER2− disease were identified by at least one prescription fill for an endocrine therapy and did not have any prescriptions for agents used to treat HER2+ disease (trastuzumab, lapatinib, pertuzumab, or ado-trastuzumab). Patients satisfying the above criteria were assessed for eligible line(s) of therapy among the first four lines of treatment for mBC. To be eligible, the treatment line (defined as the index therapy) must comprise everolimus-based therapy or chemotherapy, must have been initiated between July 20, 2012 (the US Food and Drug Administration approval date of everolimus for HR+/HER2− mBC) and March 31, 2014 (to allow for at least 3 months of potential follow-up), and be preceded by a prescription for an NSAI. In addition, patients were required to have had continuous health plan enrollment for at least 12 months prior to and at least 4 weeks after the index date, defined as the date of the initiation of the index therapy.

Eligible patients' line(s) of therapy were classified as either everolimus-based therapy or chemotherapy. Everolimus-based therapy included everolimus monotherapy or combination therapy with another mBC treatment. Chemotherapy included chemotherapy monotherapy, combination therapy of multiple chemotherapy agents, and combination with an endocrine therapy. Each line of therapy started at the index date and ended at treatment discontinuation, end of health plan enrollment, or the end of data (June 30, 2014), whichever came first.

Study Outcomes

Patient characteristics included age and insurance type (Medicare Advantage, Medicare Supplemental, or primary commercial insurance) at index date, de novo status at mBC diagnosis, time from initiation of last adjuvant endocrine therapy to mBC diagnosis (in months), number of organ-level metastatic sites, Charlson Comorbidity Index (CCI) [27] measured based on medical claims recorded in the 12 months prior to the index date (defined as baseline period), and use of chemotherapy for mBC prior to the index date.

Cost outcomes included all-cause, BC-related, and AE-related medical costs associated with inpatient, outpatient, emergency room (ER), and other medical services. All-cause medical costs included total costs reimbursed by insurers and the out-of-pocket costs incurred by patients (i.e., copayments, coinsurance, and deductible) for any medical services used during the studied line of therapy. BC-related medical costs were defined as amounts paid for medical services that were associated with a diagnosis of BC

(ICD-9-CM code 174.xx) or a secondary neoplasm (ICD-9-CM codes 196.xx-197.xx, 198.0, 198.1, 198.3-198.7, 198.81, or 198.89), and AE-related medical costs were defined as amounts paid for medical services associated with a diagnosis for a medical condition listed as AEs associated with everolimus-based therapy or chemotherapy (see Table S1 in the supplementary material). Total medical costs were reported on a per-patient-per-month (PPPM) basis to account for varying therapy durations and were inflated to 2014 US dollars using the medical care component of the Consumer Price Index (CPI).

Healthcare resource utilization included all-cause and AE-related utilization during the studied line of therapy. All-cause outcomes included the number of emergency care visits (defined as inpatient hospitalizations and ER visits), inpatient hospitalizations, days of inpatient hospitalization, ER visits, outpatient visits, BC-related outpatient visits (defined as 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). AE-related resource utilization was defined as use of inpatient, ER, outpatient, or other medical services that were associated with a diagnosis for an AE associated with everolimus-based therapy or chemotherapy (see Table S1 in the supplementary material). Healthcare resource utilization was also summarized on a PPPM basis.

Statistical Analyses

Patient baseline characteristics were compared between everolimus-based therapy and chemotherapy for each line of therapy using Wilcoxon rank-sum tests for continuous variables and Chi square tests for categorical variables.

Medical costs were compared between everolimus-based therapy and chemotherapy by line of therapy (unadjusted) and pooling all lines (adjusted), and reported as cost differences with *P* values. Unadjusted comparisons were conducted using Wilcoxon rank-sum tests. Multivariable-adjusted analyses employed 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 resampling technique with 499 iterations. Multivariable models adjusted for differences in patient baseline characteristics. As a sensitivity analysis, the cost analysis was replicated among a subgroup of patients receiving capecitabine monotherapy.

Healthcare resource utilization was compared between everolimus-based therapy and chemotherapy by line of therapy (unadjusted) and pooling all lines (adjusted) using incidence rate ratios (IRRs), estimated using GLMs with a log link and Poisson distribution. For unadjusted and adjusted analyses, *P* values were estimated using a non-parametric bootstrap resampling technique with 499 iterations. Multivariable models adjusted for differences in patient baseline characteristics.

All statistical analyses were conducted using SAS Version 9.3 (SAS Institute, Inc., Cary, NC, USA) software. A two-sided alpha error of 0.05 was used to determine statistical significance.

Compliance with Ethics Guidelines

The patient data were de-identified and complied with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act. Ethical review was not required.

RESULTS

A total of 925 eligible elderly women with HR+/HER2− mBC who received everolimus-based therapy or chemotherapy as their index treatment in at least one of their first four lines of therapy for mBC were selected, including 230 patients who contributed 240 everolimus-based therapy lines and 737 patients who contributed 939 chemotherapy lines. Among all patients treated with chemotherapy, a subgroup of 169 patients contributed 176 capecitabine monotherapy lines (Fig. 1). Patients treated with

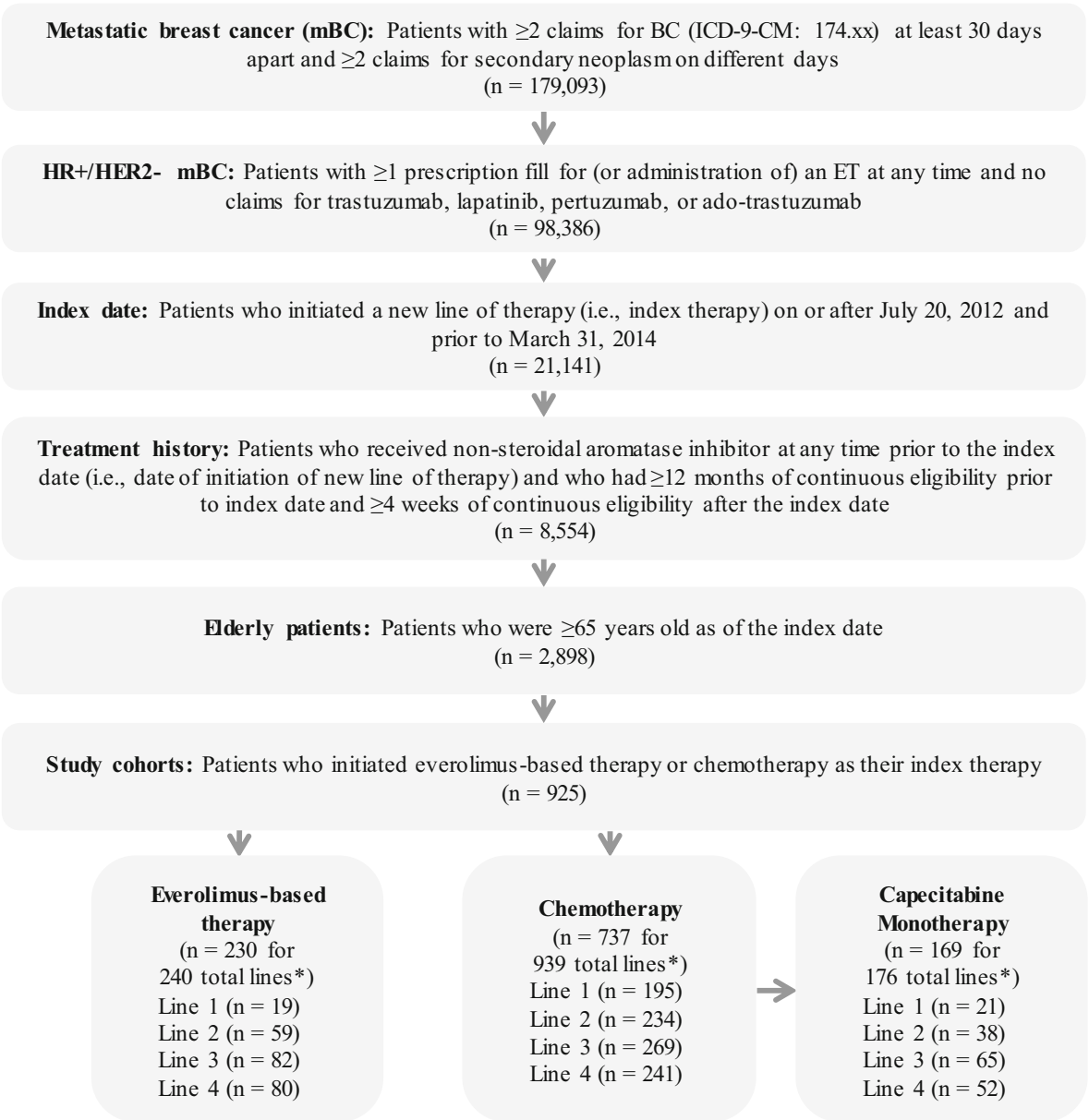

Fig. 1 Flowchart of patient selection criteria. *Asterisk* total lines of therapy may exceed number of patients if patients receive more than one line of the same therapy type. *BC* breast cancer, *ET* endocrine therapy, *ICD-9-DM* the international classification of diseases, ninth revision, clinical modification

Table 1 Comparison of patient baseline characteristics

	Line 1		Line 2		Line 3		Line 4	
	Everolimus (*N* = 19)	**Chemotherapy (*N* = 195)**	**Everolimus (*N* = 59)**	**Chemotherapy (*N* = 234)**	**Everolimus (*N* = 82)**	**Chemotherapy (*N* = 269)**	**Everolimus (*N* = 80)**	**Chemotherapy (*N* = 241)**
Descriptive characteristics								
Age at index date (years), mean ± SD [median]	73.8 ± 5.5 [73.5]	73.4 ± 5.6 [72.7]	74.3 ± 7.1 [73.2]	73.3 ± 6.1 [72.7]	72.7 ± 5.7 [71.8]	72.6 ± 5.8 [71.6]	73.5 ± 6.9 [71.6]	73.0 ± 6.1 [71.9]
Insurance type, *n* (%)								
Medicare advantage	3 (15.8%)	5 (2.6%)*	5 (8.5%)	9 (3.8%)	0 (0.0%)	14 (5.2%)*	1 (1.3%)	7 (2.9%)
Medicare supplemental	12 (63.2%)	148 (75.9%)	41 (69.5%)	174 (74.4%)	66 (80.5%)	195 (72.5%)	63 (78.8%)	181 (75.1%)
Primary commercial insurance	4 (21.1%)	42 (21.5%)	13 (22.0%)	51 (21.8%)	16 (19.5%)	60 (22.3%)	16 (20.0%)	53 (22.0%)
mBC characteristics[a], *n* (%)								
De novo	1 (5.3%)	9 (4.6%)	19 (32.2%)	41 (17.5%)*	25 (30.5%)	75 (27.9%)	19 (23.8%)	74 (30.7%)
Non-de novo	17 (89.5%)	186 (95.4%)	33 (55.9%)	187 (79.9%)***	48 (58.5%)	162 (60.2%)	48 (60.0%)	132 (54.8%)
Type of mBC unknown	1 (5.3%)	0 (0.0%)	7 (11.9%)	6 (2.6%)**	9 (11.0%)	32 (11.9%)	13 (16.3%)	35 (14.5%)
Number of organ-level metastatic sites, mean ± SD [median]	1.4 ± 1.3 [1]	1.2 ± 0.9 [1]	1.6 ± 1.2 [1]	1.5 ± 1.2 [1]	1.7 ± 1.0 [1]	1.7 ± 1.2 [2]	1.7 ± 1.1 [2]	1.8 ± 1.3 [2]
CCI, mean ± SD [median]	10.3 ± 2.0 [10]	9.4 ± 1.5 [9]	9.3 ± 1.2 [9]	9.5 ± 1.5 [9]	9.2 ± 1.3 [9]	9.3 ± 1.3 [9]	9.1 ± 1.1 [9]	9.3 ± 1.3 [9]
Prior use of chemotherapy for mBC, *n* (%)	0 (0.0%)	0 (0.0%)	4 (6.8%)	89 (38.0%)***	14 (17.1%)	148 (55.0%)***	35 (43.8%)	171 (71.0%)***
Time from initiation of last adjuvant endocrine therapy to								
mBC diagnosis (months), mean ± SD [median]	23.2 ± 27.3 [8.0]	32.8 ± 29.0 [23.8]	26.4 ± 29.7 [14.8]	24.2 ± 25.5 [15.4]	21.7 ± 23.3 [13.6]	23.3 ± 24.3 [15.1]	14.0 ± 16.0 [8.0]	22.3 ± 21.8 [13.6]

BC breast cancer, *CCI* Charlson comorbidity index, *mBC* metastatic breast cancer, *SD* standard deviation

* $P < 0.05$, ** $P < 0.01$, *** $P < 00.1$

[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 BC 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, they are considered to have unknown mBC type

everolimus-based therapy or chemotherapy had generally similar baseline characteristics across lines of therapy (Table 1). The mean age of both groups was approximately 73 years. Both groups had similar proportions of de novo and non-de novo mBC with the exception of Line 2, in which a significantly higher proportion of patients treated with chemotherapy had non-de novo mBC (79.9% vs. 55.9%, $P < 0.001$). A lower proportion of patients treated with everolimus-based therapy had prior use of chemotherapy for mBC for Lines 2–4 (Line 2: 6.8% vs. 38.0%; Line 3: 17.1% vs. 55.0%; Line 4: 43.8% vs. 71.0%, respectively; all $P < 0.001$) compared with patients treated with chemotherapy. The number of metastatic sites, time from initiation of last adjuvant endocrine therapy to mBC diagnosis, and burden of comorbidities were not significantly different between the two groups.

Over the first four lines of therapy, total PPPM all-cause medical service costs were lower among patients treated with everolimus-based therapy compared with patients treated with chemotherapy (Table 2). Specifically, patients treated with everolimus-based therapy incurred PPPM costs ranging from $2954 (Line 4) to $4483 (Line 1). In contrast, PPPM costs ranged

Table 2 Comparison of medical service costs

Costs (in 2014 $), mean ± SD	Line 1			Line 2		
	Everolimus (*N* = 19)	Chemotherapy (*N* = 195)	Unadjusted difference	Everolimus (*N* = 59)	Chemotherapy (*N* = 234)	Unadjusted difference
Total all-cause medical service costs	4483 ± 5706	7259 ± 12,147	2776	4209 ± 7850	6035 ± 11,612	1827**
Inpatient costs	2380 ± 5692	2719 ± 9523	339	2038 ± 6381	2824 ± 10,497	786
Emergency room costs	340 ± 1131	163 ± 622	−177	40 ± 139	63 ± 195	23
Outpatient costs	1622 ± 1546	4168 ± 7309	2546*	2032 ± 3835	2949 ± 4379	917***
Other medical service costs	141 ± 307	209 ± 697	68	99 ± 339	200 ± 679	101
Total BC-related medical service costs	2583 ± 4842	4679 ± 10,919	2096	2705 ± 4527	3824 ± 8316	1119
Inpatient costs	1375 ± 4885	1899 ± 8165	524	1008 ± 2784	1903 ± 7737	895
Emergency room costs	68 ± 219	22 ± 128	46	3 ± 17	8 ± 51	6
Outpatient costs	1016 ± 1122	2649 ± 6801	1633	1672 ± 3705	1831 ± 2993	159
Other medical service costs	125 ± 301	110 ± 555	−15	23 ± 77	82 ± 354	59
AE-related medical service costs	792 ± 1231	2710 ± 8968	1918	1540 ± 5480	2048 ± 7397	508

Costs (in 2014 $), mean ± SD	Line 3			Line 4			Pooled (lines 1-4)
	Everolimus (*N* = 82)	Chemotherapy (*N* = 269)	Unadjusted difference	Everolimus (*N* = 80)	Chemotherapy (*N* = 241)	Unadjusted difference	Adjusted difference
Total all-cause medical service costs	3077 ± 4649	10,268 ± 69,643	7190***	2954 ± 3833	6731 ± 24,018	3777**	4007**
Inpatient costs	1187 ± 3195	7041 ± 69,050	5854	1214 ± 2958	3261 ± 20,379	2047	1994**
Emergency room costs	73 ± 187	147 ± 595	74	90 ± 298	187 ± 1151	97	44
Outpatient costs	1764 ± 3427	2844 ± 4531	1080***	1558 ± 2302	3085 ± 5235	1527***	1402**
Other medical service costs	54 ± 138	236 ± 1201	182	92 ± 263	198 ± 707	106	120**
Total BC-related medical service costs	1982 ± 2972	8433 ± 69,385	6452*	1930 ± 2983	5274 ± 23,212	3344*	3129**
Inpatient costs	832 ± 2634	6260 ± 68,892	5428	615 ± 2103	2628 ± 19,603	2013	1883**
Emergency room costs	22 ± 83	60 ± 430	39	42 ± 171	43 ± 532	0	2
Outpatient costs	1101 ± 1505	1989 ± 3779	887**	1202 ± 2103	2509 ± 5110	1307**	913**
Other medical service costs	27 ± 102	124 ± 718	97	70 ± 249	94 ± 465	24	48
AE-related medical service costs	697 ± 2841	6200 ± 67,185	5502*	1035 ± 2746	1919 ± 5575	884	1873**

Medical service costs include costs from medical claims that are not associated with drug administration
Difference difference of chemotherapy group and everolimus group
AE adverse event, *BC* breast cancer, *SD* standard deviation
* $P < 0.05$, ** $P < 0.01$, *** $P < 00.1$

from $6035 (Line 2) to $10,268 (Line 3) for patients treated with chemotherapy. Unadjusted differences in total PPPM medical costs between patients treated with everolimus-based therapy or chemotherapy ranged from $1827 to $7190 (Lines 2 and 4, $P < 0.01$; Line 3, $P < 0.001$). These differences in total medical costs were primarily driven by significant differences in outpatient medical costs across all four lines of therapy, which ranged from $917 (Line 2, $P < 0.001$) to $2546 (Line 1, $P < 0.05$). Similar results were obtained after pooling all lines and adjusting for differences in patients' baseline characteristics. Everolimus-based therapy was associated with significantly lower total PPPM all-cause medical

costs compared to chemotherapy (adjusted mean difference: $4007), including lower costs related to inpatient ($1994) and outpatient services ($1402; all $P < 0.01$).

In addition, patients treated with everolimus-based therapy had lower PPPM BC-related medical service costs compared with patients treated with chemotherapy (Table 2). PPPM costs ranged from $1930 (Line 4) to $2705 (Line 2) for patients treated with everolimus-based therapy and from $3824 (Line 2) to $8433 (Line 3) for patients treated with chemotherapy. The unadjusted cost differences between the two groups ranged from $1119 (Line 2) to $6452 (Lines 3 and 4, $P < 0.01$). A similar trend was observed for total PPPM BC-related medical costs after adjusting for patient's characteristics (adjusted mean difference: $3129), with significant differences in BC-related inpatient ($1883) and outpatient costs ($913; all $P < 0.01$).

Furthermore, patients treated with everolimus-based therapy incurred lower PPPM AE-related medical service costs compared to patients treated with chemotherapy (Table 2). Patients treated with everolimus-based therapy had PPPM costs ranging from $697 (Line 3) to $1540 (Line 2), compared with costs ranging from $1919 (Line 4) to $6200 (Line 3) for patients who received chemotherapy. Unadjusted cost differences between the two groups ranged from $508 (Line 2) to $5502 (Line 3, $P < 0.05$). Similarly, the adjusted results showed significant lower total PPPM AE-related medical costs for patients treated with everolimus-based therapy compared with patients treated with chemotherapy (adjusted mean difference: $1873, $P < 0.01$).

The sensitivity analysis comparing medical service costs of everolimus-based therapy and the subgroup of capecitabine monotherapy showed overall consistent findings as the main analyses (see Table S2 in the supplementary material). Multivariable models demonstrated that everolimus-based therapy was associated with significantly lower total PPPM all-cause and BC-related medical costs (adjusted mean difference: $6332 and $5769, both $P < 0.01$) compared to capecitabine monotherapy. The difference in total AE-related medical costs ($1397) was not significant.

The lower medical services costs for patients treated with everolimus-based therapy were consistent with their lower use of health resources during the studied lines of therapy (Table 3). Compared with patients treated with chemotherapy, patients treated with everolimus-based therapy had a significantly lower incidence of all-cause outpatient visits (unadjusted Line 1 IRR = 0.68; Line 2 IRR = 0.65; Line 3 IRR = 0.70; Line 4 IRR = 0.73; all $P < 0.01$) and BC-related outpatient visits (unadjusted Line 2 IRR = 0.66; Line 3 IRR = 0.62; Line 4 IRR = 0.69; all $P < 0.01$). These results were maintained after pooling all lines and adjusting for patient baseline characteristics (adjusted all-cause outpatient IRR = 0.69, $P < 0.01$; BC-related outpatient visits IRR = 0.66, $P < 0.01$). Patients treated with everolimus-based therapy also had lower utilization of other medical services (unadjusted Line 2 IRR = 0.57; Line 3 IRR = 0.54, both $P < 0.05$), a result that was maintained in multivariable-adjusted analyses (adjusted IRR = 0.65, $P < 0.01$). The use of emergency care, including inpatient admissions and days and ER visits, was not significantly different between the two groups in any line studied.

Patients treated with everolimus-based therapy also had significantly lower AE-related resource utilization than those treated with chemotherapy (Table 3; unadjusted Line 2 IRR = 0.56; Line 3 IRR = 0.51; Line 4

Table 3 Comparison of HRU

	Line 1			Line 2		
	Everolimus (*N* = 19)	Chemotherapy (*N* = 195)	Unadjusted IRR	Everolimus (*N* = 59)	Chemotherapy (*N* = 234)	Unadjusted IRR
Emergency care visits	0.282	0.217	1.30	0.130	0.146	0.89
Inpatient admissions	0.125	0.086	1.46	0.072	0.081	0.90
Inpatient days	0.565	0.706	0.80	0.572	0.612	0.94
Emergency room visits	0.157	0.132	1.19	0.058	0.066	0.88
Outpatient visits	3.875	5.659	0.68**	3.094	4.733	0.65**
BC-related outpatient visits	2.463	3.242	0.76	1.841	2.786	0.66**
Other medical services	0.737	0.724	1.02	0.453	0.797	0.57*
AE-related HRU	1.239	1.683	0.74	0.826	1.476	0.56**
Inpatient admissions	0.094	0.073	1.28	0.062	0.075	0.82
Emergency room visits	0.125	0.062	2.01	0.029	0.040	0.72
Outpatient visits	0.926	1.459	0.63	0.659	1.272	0.52 **
Other medical services	0.094	0.089	1.06	0.076	0.087	0.87

	Line 3			Line 4			Pooled (lines 1–4)
	Everolimus (*N* = 82)	Chemotherapy (*N* = 269)	Un adjusted IRR	Everolimus (*N* = 80)	Chemotherapy (*N* = 241)	Unadjusted IRR	Adjusted IRR
Emergency care visits	0.143	0.161	0.88	0.153	0.171	0.90	0.90
Inpatient admissions	0.054	0.068	0.80	0.071	0.077	0.92	0.93
Inpatient days	0.324	0.449	0.72	0.442	0.529	0.84	0.79
Emergency room visits	0.088	0.094	0.94	0.082	0.093	0.88	0.88
Outpatient visits	3.295	4.691	0.70**	3.199	4.388	0.73**	0.69**
BC-related outpatient visits	1.953	3.161	0.62**	1.998	2.884	0.69**	0.66**
Other medical services	0.348	0.649	0.54*	0.532	0.738	0.72	0.65**
AE-related HRU	0.880	1.728	0.51**	0.985	1.658	0.59**	0.59**
Inpatient admissions	0.048	0.059	0.81	0.057	0.070	0.82	0.87
Emergency room visits	0.059	0.053	1.11	0.052	0.064	0.81	0.97
Outpatient visits	0.726	1.497	0.49**	0.797	1.358	0.59**	0.56**
Other medical services	0.048	0.119	0.40	0.079	0.166	0.48	0.69

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

IRR IRR of everolimus group to chemotherapy group

AE Adverse event, *HRU* Healthcare resource utilization, *IRR* Incidence rate ratio

* $P < 0.05$, ** $P < 0.01$, *** $P < 00.1$

IRR = 0.59; adjusted IRR = 0.59; all $P < 0.01$), mainly driven by fewer AE-related outpatient visits (unadjusted Line 2 IRR = 0.52; Line 3 IRR = 0.49; Line 4 = 0.59; adjusted IRR = 0.56; all $P < 0.01$). AE-related inpatient admissions, ER visits, and other medical service visits were not significantly different between the two groups in any line studied.

DISCUSSION

Patients with mBC incur significant costs, and these costs can be compounded following treatment-related AEs. Older patients are more likely to have comorbidities that both reduce the tolerability of chemotherapy and increase the risk of developing serious AEs [13], resulting

in higher costs for managing mBC. To the best of our knowledge, this study is the first to compare medical costs and healthcare resource utilization among elderly patients with HR+/HER2− mBC receiving treatment with everolimus-based therapy or chemotherapy in a real-world setting. This study found that everolimus-based therapy was associated with significant cost savings in all-cause and BC-related medical costs compared to chemotherapy, including a subgroup of capecitabine monotherapy, driven primarily by inpatient and outpatient medical services, and significantly lower medical costs related to managing AEs. In addition, everolimus-based therapy was associated with significantly lower use of all-cause medical services relative to chemotherapy, in particular outpatient visits, BC-related outpatient visits, and other medical services, as well as lower AE-related resource utilization driven by significantly fewer AE-related outpatient visits.

The results of this study contribute novel real-world information about the elderly HR+/HER2− mBC subpopulation to an existing set of literature that has identified medical cost savings associated with everolimus-based therapy as compared to chemotherapy in a wider age range. A recent study examining medical costs in post-menopausal women with HR+/HER2− mBC treated with everolimus-based therapy or chemotherapy (mean age approximately 60 years) found that patients receiving everolimus-based therapy had $3455 lower all-cause, $2510 lower BC-related, and $1730 lower AE-related medical costs compared with those receiving chemotherapy [21]. The present study indicated that elderly patients experienced even greater medical cost savings if using everolimus-based therapy relative to chemotherapy ($4007, $3129, and $1873, respectively). The real-world results of this study confirm the findings of previous budget-impact models showing medical cost savings associated with everolimus-based therapy over chemotherapy in post-menopausal patients with HR+/HER2− mBC [28, 29]. Additionally, a recent cost-effectiveness analysis indicated that everolimus-based therapy was associated with greater gains in quality-adjusted life-years and lower lifetime costs compared to bevacizumab-based chemotherapy after initial failure of NSAIs [20].

This study's findings have important implications for the decision-making by key healthcare stakeholders, both for private payers for whom elderly patients represent a growing proportion of insured population and for Medicare, which insures the majority of the elderly in the US. The projected annual cost of BC in the US is expected to hit $36.5 billion by 2020 [30], thus developing treatment strategies to reduce costs while maintaining optimal patient outcomes is imperative. The principles of managing mBC in the elderly are similar to those in younger patients, but with special considerations linked to comorbidities and performance status. Because mBC is not curable, the main treatment goals are to minimize disease symptoms while prolonging and maintaining patients' quality of life (QoL). Avoiding AEs are important considerations in the treatment of elderly patients due to potential intolerance of drug toxicity, unintended drug interactions, and higher burden of comorbidities—all of which negatively impact QoL. Payers should consider that treatment with everolimus-based therapy is less toxic compared to chemotherapy. A network meta-analysis of randomized-controlled trials (RCTs) conducted by Generali et al. [31] compared the efficacy and safety of everolimus-based therapy versus

chemotherapy. An exploratory evaluation of the percentages of patients affected by grade 3/4 AEs showed that everolimus-based therapy was associated with fewer AEs relative to commonly-used chemotherapy regimens. This better tolerability profile observed in everolimus-based therapy is likely to translate into lower AE-related costs and less AE-related healthcare resource utilization observed in patients treated with everolimus-based therapy in the current study.

Although the current study did not compare the effectiveness of everolimus-based therapy and chemotherapy, previous real-world studies among patients with HR+/HER2− mBC have found better clinical effectiveness with everolimus-based therapy, with significantly longer overall survival, PFS, and time on treatment compared with chemotherapy [32]. However, a similar study has not been conducted focusing on elderly patients. In this study, the observed savings in medical cost and healthcare resource utilization associated with everolimus-based therapy over chemotherapy may reflect the superior disease control and fewer side effects that would otherwise require visits to physicians. Thus, the lower overall, BC-, and AE-related medical costs for everolimus-based therapy, bolstered by previous economic models, are valuable evidence for payers considering mBC treatments that can increase PFS and maintain QoL while reducing AEs as well as costs. For these reasons, everolimus-based therapy should be viewed as a more clinically- and cost-effective option relative to chemotherapy for elderly patients with HR+/HER2− mBC.

This study included some limitations related to the use of claims database. First, information on HR+/HER2− mBC was not directly available in the database; therefore, the identification of these patients had to rely on an algorithm based on a combination of different proxies. Similarly, information on lines of treatment was not directly available in the database; therefore, an algorithm was used to classify observed therapies into regimens. Certain clinical factors that might impact treatment decisions (e.g., patients' performance status may impact the use of everolimus-based therapy relative to chemotherapy) were not available within the databases and could not be adjusted for in the multivariable models. Second, the current databases include only patients who had some form of commercial insurances, for example Medicare Advantage or employer-sponsored commercial plans to supplement Medicare, i.e., they do not include patients with only Medicare insurance. Thus, the generalizability of these results to the entire Medicare population may be limited. Third, only direct medical costs were studied. Information to determine indirect costs, such as burden to caregivers, was not available in the databases. Fourth, with a focus on economic outcomes, the current study did not analyze tolerability-related outcomes. Such analyses might help shed light on the findings of AE-related medical costs and resource utilization. Future studies are needed to compare the safety profile of everolimus-based therapy and chemotherapy among elderly patients specifically. Finally, as a retrospective claims database analysis, patients were not randomized to the treatment of everolimus-based therapy and chemotherapy; therefore, unobserved confounding and patient selection bias could exist. In our multivariable analyses, we adjusted for important prognostic factors that were available in the claims databases (e.g., number of metastases and burden of comorbidities), but unobserved confounding still could exist. Only economic analyses based on a well-conducted RCT can fully address such limitations.

CONCLUSIONS

Treatment with everolimus-based therapy among elderly women with HR+/HER2− mBC was associated with lower all-cause, BC-related, and AE-related medical service costs, as well as reduced healthcare resource use compared to treatment with chemotherapy. On a PPPM basis, everolimus-based therapy was associated with adjusted total medical cost savings of $4007 compared to chemotherapy overall and $6332 compared to capecitabine monotherapy across all lines.

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REFERENCES

1. World Health Organization. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevelance worldwide in 2012. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed 26 Oct 2015.
2. Wildiers H, Kunkler I, Biganzoli L, Fracheboud J, Vlastos G, Bernard-Marty C, et al. Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. Lancet Oncol. 2007;8(12):1101–15.
3. Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E, Group EGW. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol ESMO. 2012; 23(Suppl 7):vii11–9.
4. Lu J, Steeg PS, Price JE, Krishnamurthy S, Mani SA, Reuben J, et al. Breast cancer metastasis: challenges and opportunities. Cancer Res. 2009;69(12):4951–3.
5. Muss HB, Busby-Whitehead J. Older women with breast cancer: slow progress, great opportunity, now is the time. J Clin Oncol. 2011;29(35):4608–10.

6. van de Water W, Markopoulos C, van de Velde CJ, Seynaeve C, Hasenburg A, Rea D, et al. Association between age at diagnosis and disease-specific mortality among postmenopausal women with hormone receptor-positive breast cancer. JAMA. 2012;307(6):590–7.

7. Riseberg D. Treating Elderly patients with hormone receptor-positive advanced breast cancer. Clin Med Insights Oncol. 2015;9:65–73.

8. Yardley DA. Taxanes in the elderly patient with metastatic breast cancer. Breast cancer. 2015;7:293–301.

9. Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LA, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst. 2014;106(5).

10. Hutchins LF, Unger JM, Crowley JJ, Coltman CA Jr, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med. 1999;341(27):2061–7.

11. National Comprehensive Cancer Network. Breast Cancer, Version 2.2015: National Comprehensive Cancer Network (NCCN); 2015 [21 May 2015]. 184. Available from: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed 26 Oct 2015.

12. Vera-Llonch M, Weycker D, Glass A, Gao S, Borker R, Qin A, et al. Healthcare costs in women with metastatic breast cancer receiving chemotherapy as their principal treatment modality. BMC Cancer. 2011;11:250.

13. Aapro M, Bernard-Marty C, Brain EG, Batist G, Erdkamp F, Krzemieniecki K, et al. Anthracycline cardiotoxicity in the elderly cancer patient: a SIOG expert position paper. Ann Oncol. 2011;22(2):257–67.

14. Baselga J, Campone M, Piccart M, Burris HA, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. New Engl J Med. 2012;366(6):520–9.

15. Baselga J, Campone M, Piccart M, Burris HA 3rd, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 2012;366(6):520–9.

16. Pritchard KI, Burris HA, 3rd, Ito Y, Rugo HS, Dakhil S, Hortobagyi GN, et al. Safety and efficacy of everolimus with exemestane vs. exemestane alone in elderly patients with HER2-negative, hormone receptor-positive breast cancer in BOLERO-2. Clin Breast Cancer. 2013;13(6):421–32 e8.

17. Rugo HS, Pritchard KI, Gnant M, Noguchi S, Piccart M, Hortobagyi G, et al. Incidence and time course of everolimus-related adverse events in postmenopausal women with hormone receptor-positive advanced breast cancer: insights from BOLERO-2. Ann Oncol. 2014;25(4):808–15.

18. Pawaskar MKS, Dalvi T, et al.Health care utilization and costs among HER2-negative, HR-positive, elderly women with metastatic breast cancer in the United States, abstr ASCO Annual Meeting, Chicago, IL. J Clin Oncol. 2013 (suppl; abstr e11571)

19. Xie J, Hao Y, Zhou ZY, Qi CZ, De G, Gluck S. Economic evaluations of everolimus versus other hormonal therapies in the treatment of HR/HER2 Advanced Breast Cancer From a US Payer Perspective. Clin Breast Cancer. 2015;15:e263–76.

20. Kourlaba G, Rapti V, Alexopoulos A, Relakis J, Koumakis G, Chatzikou M, et al. Everolimus plus exemestane versus bevacizumab-based chemotherapy for second-line treatment of hormone receptor-positive metastatic breast cancer in Greece: An economic evaluation study. BMC Health Serv Res. 2015;15:307.

21. Li N, Hao Y, Koo V, Fang A, Peeples M, Kageleiry A, et al. 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. 2016 NCCN Annual Meeting; Hollywood, FL during March 31-April 2, 2016.

22. Gelmon K, Chan A, Harbeck N. The role of capecitabine in first-line treatment for patients with metastatic breast cancer. Oncologist. 2006;11(Suppl 1):42–51.

23. Wang Y, Yang H, Wei JF, Meng L. Efficacy and toxicity of capecitabine-based chemotherapy in patients with metastatic or advanced breast cancer: results from ten randomized trials. Curr Med Res Opin. 2012;28(12):1911–9.

24. Blum JL, Barrios CH, Feldman N, Verma S, McKenna EF, Lee LF, et al. Pooled analysis of individual patient data from capecitabine monotherapy clinical trials in locally advanced or metastatic breast cancer. Breast Cancer Res Treat. 2012;136(3):777–88.

25. Swallow E, Zhang J, Thomason D, Tan RD, Kageleiry A, Signorovitch J. Real-world patterns of endocrine therapy for metastatic hormone-receptor-positive (HR+)/human epidermal growth factor receptor-2-negative (HER2-) breast cancer patients in the United States: 2002–2012. Curr Med Res Opin. 2014;30(8):1537–45.

26. Whyte JL, Engel-Nitz NM, Teitelbaum A, Gomez Rey G, Kallich JD. An evaluation of algorithms for identifying metastatic breast, lung, or colorectal cancer in administrative claims data. Med Care. 2015;53(7):e49–57.

27. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.

28. Xie J, Diener M, De G, Yang H, Wu EQ, Namjoshi M. Budget impact analysis of everolimus for the treatment of hormone receptor positive, human epidermal growth factor receptor-2 negative (HER2-) advanced breast cancer in the United States. J Med Econ. 2013;16(2):278–88.

29. Lewis L, Taylor M, Suriya Ertugyrovna Y, Kuanysh Shadybayevich N, Kaldygul Kabakovna S, Ramil Zufarovich A. Budget impact analysis of everolimus for the treatment of hormone receptor positive, human epidermal growth factor receptor-2 negative (HER2-) advanced breast cancer in Kazakhstan. J Med Econ. 2015;18(3):189–99.

30. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010–2020. J Natl Cancer Inst. 2011;103(2):117–28.

31. Generali D, Venturini S, Rognoni C, Ciani O, Pusztai L, Loi S, et al. A network meta-analysis of everolimus plus exemestane versus chemotherapy in the first- and second-line treatment of estrogen receptor-positive metastatic breast cancer. Breast Cancer Res Treat. 2015;152(1):95–117.

32. Li N, Hao Y, Xie J, Lin PL, Koo V, Ohashi E, et al. Everolimus-based therapy versus chemotherapy among patients with HR+/HER2− metastatic breast cancer: comparative effectiveness from a chart review study. Int J Breast Cancer. 2015;2015:1–9.