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Breast Cancer

Real-World Patterns of Everolimus Use in Patients with Metastatic Breast Cancer

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

Key Words. Everolimus • Metastatic breast cancer • Hospitalization • ER visit • Patterns of use • Adverse events

Abstract

Background. There is limited literature on patterns of everolimus use and subsequent hospitalizations and emergency room (ER) visits in real-world clinical practice. In this study, we describe patterns of everolimus use and hospitalizations and ER visits in a large cohort of patients with breast cancer (BC).

Materials and Methods. Patients with BC treated with everolimus were identified in the MarketScan database from 2009 to 2016. The pattern of everolimus use and frequency of associated ER visits and hospitalizations during treatment (between the first claim and 30 days after the last claim for everolimus) were identified. Descriptive statistics and regression models were used.

Results. A total of 3,556 everolimus users were identified (median age of 60 years; median days of use, 112). The initial prescribed dose was 10 mg in 74.8% of the patients. Compared with the initial dose, 23.5% of patients had a dose change. Forty-six percent of patients were hospitalized or had an ER visit during the treatment with everolimus. Age greater than 71, higher comorbidity score, treatment year prior to 2012, and lower initial dose were found to be significantly associated with ER visit/hospitalization in the regression models.

Conclusions. A significant proportion of patients receiving everolimus had an ER visit or hospitalization during the use of everolimus. These results provide data regarding risks and benefits of treatment with everolimus. These results will be helpful in identifying patients at higher risk of hospitalizations or ER visits and facilitate evidence-based decision making to avoid serious complications. ***The Oncologist*** 2020;25:937–942

Implications for Practice: Everolimus, a mammalian target of rapamycin inhibitor, is approved in combination with exemestane in patients with hormone receptor–positive tumors previously treated with anastrozole or letrozole. As new drugs become available, it is crucial to understand the adverse events and potential complications associated with the use of such drugs in the general population, outside of the controlled clinical trial setting. This study describes the patterns of everolimus use and adverse events, including hospitalization and emergency room visits, in a large cohort of patients with metastatic breast cancer in routine practice.

Introduction

The number of women living with metastatic breast cancer (mBC) in the U.S. was estimated to be 138,622 in 2013 [1]. It is projected that the prevalence of mBC will increase to 168,292 in 2020 [1]. Although mBC is still an incurable condition, the increasing number of patients living with mBC is likely due to improved therapies and better survival [2]. In a contemporary nationally representative cohort, the 5-year breast cancer–specific survival rate for patients diagnosed with stage IV de novo was found to be 39% (ranging from 35% to 43%) [3].

Hormone receptor (HR)–positive and human epidermal growth factor receptor 2 (HER2)–negative tumors represent the most common breast cancer subtype, accounting for close to 70% of all breast cancer cases in the US [4]. The

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goal of treatment for patients with mBC is palliative and focuses on prolonging life and improving quality of life [1]. Among patients with metastatic HR-positive and HER2-negative tumors, endocrine therapy is the cornerstone of treatment [5–8]. Unfortunately, despite initial treatment benefit, almost all patients develop resistance to endocrine therapy. Targeted therapy with everolimus, a mammalian target of rapamycin inhibitor, has been shown to enhance the efficacy of endocrine therapies and potentially reverse endocrine resistance. In the TAMRAD study, a phase II clinical trial evaluating the use of tamoxifen in combination with everolimus versus tamoxifen alone among patients with HR+/HER2− mBC previously treated with endocrine therapy, those receiving the combination had a higher clinical benefit rate (61% vs. 42%, p = .045) and longer time to progression (8.6 months vs. 4.5 months, p = .002) [9]. The BOLERO-2 [10] study, a large phase III clinical trial (n = 724), enrolled postmenopausal women with HR+/HER2− mBC previously treated with nonsteroidal aromatase inhibitors and randomized them to receive exemestane and everolimus or exemestane and placebo. Patients receiving everolimus had a significantly longer progression-free survival compared with those treated with placebo (7.8 months vs. 3.2 months, $p \leq .0001$). Patients treated in the everolimus arm experienced more adverse events, including stomatitis, fatigue, nausea, dyspnea, rash, pneumonitis, and anemia [10]

Given the improved outcomes associated with everolimus, in July 2012, the U.S. Food and Drug Administration (FDA) approved its use in combination with exemestane for the treatment of postmenopausal women with advanced HR+ and HER2− that were previously treated with letrozole or anastrozole [11]. Since then, everolimus has been incorporated into clinical practice, and its use is supported by current treatment guidelines [6]. To date, there is limited literature on patterns of everolimus use and adverse events associated with its use in real-world clinical practice. In this study including a large cohort of patients with mBC, we sought to describe the patterns of everolimus use. In addition, we describe the rates of hospitalizations and emergency room (ER) visits that patients experienced while receiving this therapy.

Materials and Methods

Study Design and Data Set

We conducted a retrospective cohort study using the Truven Health MarketScan Commercial Claims and Encounters database [12]. This large, nationwide employment-based database includes medical claims data of employees and dependents from approximately 45 large employers covered by more than 100 payers. The database includes health plans for employees and dependents receiving insurance through large, medium, and small-sized firms. For this study, we used claims collected from 2008 to 2016 to identify individuals who received everolimus treatment and were diagnosed with breast cancer (BC).

Cohort Selection and Definitions

National Drug Code numbers in pharmacy claim files were used to identify patients who received everolimus treatment. In total, 7,640 patients were identified between 2009 and 2016. The date of the first everolimus claim was used as the index date. Among these patients, a BC diagnosis was identified by diagnosis codes (International Classification of Diseases [ICD-9] and ICD-10 174.xx/C50) in one inpatient claim or two outpatient claims that were more than 30 days apart. Patients with a BC diagnosis any time before or within 30 days after the index date were identified as breast cancer cases. The cohort was then limited by excluding patients aged younger than 18. Given our intention to study the impact of comorbidities on the use and adverse events associated with everolimus, we limited our cohort to individuals with continuous enrollment during the 6 months before the index date.

Measures and Outcomes

The baseline characteristics assessed were gender, age, geographic region (northeast, north central, south, or west), and insurance type (health maintenance organization [HMO], preferred provider organization [PPO], or another plan type). Deyo's adaptation of Charlson's comorbidity score [13] was calculated using claims from 6 months before the index date. We described everolimus treatment patterns, including dose and duration of treatment, and the endocrine therapies used in combination with it. We also evaluated chemotherapy administration prior to everolimus use. The duration of treatment was defined as the time from the first claim of everolimus to the 30th day past the end date of the last everolimus claim. We evaluated any hospitalization (HSP) and ER visits during the everolimus treatment as an outcome. We explored the most common diagnosis codes associated with the HSP/ER. Additionally, because pneumonitis is a serious known adverse event, and mucositis or stomatitis is a known concern associated with everolimus use, we identified the percentage of patients that had claims for these two adverse events associated with HSP/ER.

Descriptive statistics were used for baseline characteristics. The time to event was calculated from the index date to the date of HSP/ER or the last month of enrollment through the end of the study period, which was December 31, 2016. Multivariable Cox regression models were used to determine the association between patient characteristics and HSP/ER. Dose modification after the starting dose was modeled as a time-varying covariate, that is, patients were initially considered "no change" and then "increased" or "decreased" if their dose was changed until end of follow-up. Results are expressed in hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical analyses were conducted used SAS Enterprise Guide 6 (SAS Institute, Cary, NC) with an a priori significance level of 0.05. The study protocol was determined exempt by the Institutional Review Board of The University of Texas MD Anderson Cancer Center.

Results

Between 2009 and 2016, there were 3,844 patients with at least one everolimus claim and diagnosis of breast cancer, with a total of 3,556 patients meeting our inclusion and exclusion criteria, as shown in supplemental online

Table 1. Baseline patient demographics and clinical characteristics of patients with breast cancer treated with everolimus (*n* = 3,556)

Characteristics	*n* (%)
Age, years	
25–54	1,055 (29.7)
55–64	1,407 (39.6)
65–70	463 (13.0)
71+	631 (17.7)
Year of treatment	
2009–2011	117 (3.3)
2012	868 (24.4)
2013	923 (26.0)
2014	829 (23.3)
2015	479 (13.5)
2016	340 (9.6)
Gender	
Female	3,530 (99.3)
Male	26 (0.7)
Geographic region	
Northeast	717 (20.2)
North Central	830 (23.3)
South	1,288 (36.2)
West	672 (18.9)
Unknown	49 (1.4)
Insurance type	
PPO	1,966 (55.3)
HMO	377 (10.6)
Other	1,213 (34.1)
Deyo comorbidity score	
0	2,624 (74.8)
1	629 (17.8)
2	303 (8.2)
Received chemotherapy prior to everolimus claim	
No	1,438 (40.4)
Yes	2,118 (59.6)
Initial dose, mg	
10	2,660 (74.8)
7.5	125 (3.5)
5	682 (19.2)
2.5	89 (2.5)
Dose change during treatment	
No change	2,719 (76.5)
Decrease	600 (16.8)
Increase	237 (6.6)

Abbreviations: HMO, health maintenance organization; PPO, preferred provider organization.

Table 2. Proportion of adverse events identified during everolimus treatment (*n* = 3,556)

	HSP/ER (*n* = 1,623)	
Characteristics	*n* (%)	*p* value
Age, years		
25–54	457 (43.3)	<.01
55–64	629 (44.7)	
65–70	202 (43.6)	
71+	335 (53.1)	
Year of treatment		
2009–2011	68 (58.1)	<.01
2012	418 (48.2)	
2013	421 (45.6)	
2014	360 (43.4)	
2015	225 (47.0)	
2016	131 (38.5)	
Gender		
Female	1,609 (45.6)	.39
Male	14 (53.9)	
Geographic region		
Northeast	320 (44.6)	.03
North central	404 (48.7)	
South	603 (46.8)	
West	279 (41.5)	
Unknown	17 (34.7)	
Insurance type		
PPO	1,129 (44.7)	.43
HMO	309 (45.9)	
Other	185 (47.1)	
Deyo comorbidity score		
0	1,129 (43.0)	<.01
1	309 (49.1)	
2+	185 (61.1)	
Received chemotherapy		
No	637 (44.3)	.18
Yes	986 (46.6)	
Initial dose, mg		
10	1,210(45.5)	.16
7.5	55 (44.0)	
5	307 (45.0)	
2.5	51 (57.3)	
Dose change during treatment		
No change	1,220 (44.9)	.16
Decrease	295 (49.2)	
Increase	108 (45.6)	

Abbreviations: ER, emergency room; HMO, health maintenance organization; HSP, hospitalization; PPO, preferred provider organization.

Figure 1. Baseline patient and clinical characteristics are presented in Table 1. The median age of the cohort was 60 years (range, 25–96). Most of the patients (74.8%) had a comorbidity score of zero and were insured by a PPO plan (55.3%). A striking increase in everolimus use was identified from 2012 onward, as expected by the FDA approval of

Table 3. Multivariate Cox model results to evaluate the association between patient characteristics and adverse outcomes among 3,556 patients with breast cancer treated with everolimus

Characteristics	HSP/ER, HR (95% CI)
Age, years	
25–54	Ref.
55–64	1.02 (0.91–1.16)
65–70	0.98 (0.83–1.16)
71+	**1.18 (1.02–1.37)**
Year of treatment	
2012	Ref.
2009–2011	**1.33 (1.02–1.72)**
2013	0.88 (0.77–1.01)
2014	0.88 (0.77–1.02)
2015	0.92 (0.78–1.08)
2016	0.94 (0.77–1.14)
Gender	
Female	Ref.
Male	1.09 (0.64–1.85)
Geographic region	
Northeast	Ref.
North central	1.15 (0.99–1.34)
South	1.12 (0.97–1.28)
West	0.93 (0.79–1.10)
Unknown	0.86 (0.54–1.36)
Insurance type	
PPO	Ref.
HMO	1.06 (0.90–1.25)
Other	1.04 (0.93–1.16)
Deyo comorbidity score	
0	Ref.
1	**1.25 (1.10–1.43)**
2	**1.82 (1.55–2.13)**
Received chemotherapy	
No	Ref.
Yes	1.10 (0.99–1.22)
Initial dose, mg	
10	Ref.
7.5	0.99 (0.75–1.31)
5	0.98 (0.86–1.12)
2.5	**1.39 (1.05–1.86)**
Dose change during treatment[a]	
No change	Ref.
Decrease	1.11 (0.95–1.30)
Increase	1.15 (0.87–1.53)

Boldface indicates $p < .05$.
[a]Time-dependent covariate.
Abbreviations: CI, confidence interval; ER, emergency room; HMO, health maintenance organization; HR, hazard ratio; HSP, hospitalization; PPO, preferred provider organization; Ref., reference.

everolimus for advanced BC in 2012, with a decrease in use observed in 2015 and 2016.

The median days of everolimus supply was 112 days (interquartile range, 56–196). Although 17.9% of patients had only one claim for everolimus, 33.3% of patients had six or more claims. The most common starting dose of everolimus was 10 mg and was used by 74.8% of patients; 19.2% of patients were initially treated with 5 mg. The majority of patients (76.5%) did not experience dosing changes during the duration of their therapy, whereas 16.8% had a dose reduction, and 6.6% had a dose increase. Among those that required a dose reduction, 89.8% received an initial dose of 10 mg. Exemestane was the most commonly coadministered drug used in 69.4% of patients; anastrozole, tamoxifen, letrozole, and fulvestrant were coadministered with everolimus in 3.4%, 3.5%, 5.3%, and 0.3% of patients, respectively. No endocrine therapy was identified in 24% of patients. We also observed that 59.6% of the patients in our cohort had a claim for chemotherapy in the year prior to everolimus use.

A total of 1,623 (45.6%) patients had HSP/ER claims during everolimus treatment, as shown in Table 2. Of these, 778 (19.8%) had one HSP/ER visit and 845 (25.8%) had multiple HSP/ER visits. The median time from the initial everolimus claim to HSP/ER visit was 61 days (interquartile range, 27–132). The most common diagnosis codes associated with such visits were hypertension (10.7%), pneumonia (9.7%), pleural effusion (8.3%), dehydration (8.2%), and shortness of breath (7.1%; supplemental online Table 1). About 1.1% of the HSP/ER had corresponding diagnosis of mucositis or stomatitis, and 0.1% of the HSP/ER had a diagnosis of pneumonitis.

Table 3 presents the results of multivariable Cox regression models used to identify patient characteristics associated with hospitalization or ER visits. Comorbidity index was significantly associated with HSP/ER. There was an increased risk of HSP/ER for patients with a Deyo score of 1 as compared with 0 (HR, 1.25; 95% CI, 1.10–1.43) and for patients with a score of ≥2 when compared with 0 (H, 1.82; 95% CI, 1.55–2.13). There was an increased risk of HSP/ER in patients aged 71+ (HR, 1.18; 95% CI, 1.02–1.37) compared with patients aged 25–54. Patients with a lower initial dose (i.e., 2.5 mg) had a higher risk of HSP/ER when compared with patient with initial dose of 10 mg (HR, 1.39; 95% CI, 1.05–1.86). The change in everolimus dose was not associated with HSP/ER. The year of treatment with everolimus prior to 2012 also showed an increased risk of HSP/ER as compared with patients being treated in 2012 (HR, 1.33; 95% CI, 1.02–1.72).

Discussion

In this large study including 3,556 everolimus-treated patients with mBC, most patients (69.4%) were treated with the combination of everolimus and exemestane, consistent with the current indication. About half of the patients had a hospitalization or ER visit during everolimus treatment. Age greater than 71, higher comorbidity score, and lower initial dose were associated with increased risk of HSP/ER. Interestingly, we observed there was a trend of fewer HSP/ER in more recent years, with the percentage decreasing from 58% in

2009–2011 to 39% in 2016. This decrease may suggest that if those admissions were related to everolimus toxicities, maybe the management of adverse events improved over the years, and those were likely managed in the outpatient setting, possibly avoiding ER visits or hospitalizations. Two common adverse effects reported in BOLERO-2 and TAMRAD were stomatitis (8% and 56%) and pneumonitis (3% and 17%) in the treatment arms. These rates contrast with the low rate of stomatitis and pneumonitis seen in our study (1.1% and 0.1%). It is likely that the higher rate of these everolimus-related complications seen in the pivotal trials is related to a higher identification rate due to the close monitoring of clinical trial participants. Furthermore, we only report here the percentage of patients with a diagnosis of stomatitis and pneumonitis identified during an ER visit or hospitalization, likely identifying severe cases. Grade 3 or 4 stomatitis and pneumonitis were reported in 8% and 1% patients in BOLERO-2 trial and 11% and 2% in TAMRAD and are more comparable to the rates seen in our study.

Guérin et al. [14] reported the treatment patterns and factors associated with everolimus treatment among 902 postmenopausal women with HR+/HER2− mBC using the Truven MarketScan and IMS Health PharMetrics databases. Similar to our results, they observed that approximately 80% of patients initiated everolimus at a dose of 10 mg daily and noted that less than 5% of patients experienced a dose increase relative to the index dose, whereas approximately 20% of patients experienced a dose reduction. This percentage of patients with dose reductions is considerably lower than that of BOLERO-2 trial (67%), which could be attributed to the differences in patient characteristics and study design as well as differences in management of adverse events in a real-world versus clinical-trial setting versus the strict protocol-mandated dose reduction recommendations. Among patients who experienced a dose decrease, the majority initiated a starting dose of 10 mg daily. Data on toxicities were not reported. In our results, we report the number of hospitalizations and ER visits during the treatment with everolimus along with the most common associated diagnoses.

We observed a relationship between older age, a higher comorbidity score, and HSP/ER. This finding is not surprising; it is likely that patients with higher comorbidity index at baseline were sicker or had worse performance status and therefore required an ER visit or hospitalization. Although it is possible that dose changes occurred as a result of toxicity, we were unable to determine any such association. Patients treated with an initial dose of 2.5 mg had an increased risk of hospitalization or ER compared with patients who received an initial dose of 10 mg. We cannot exclude that patients were started at lower doses because of poor overall clinical condition and thus were more likely to have hospitalization or ER visits. Given the nature of our claims-based study and the variables available in the data set, no information on performance status, overall clinical condition, or extent of disease was available to correlate dose with clinical condition.

The median age in our cohort was 60 years, which is slightly younger compared with the median age of patients in the TAMRAD (64) and BOLERO-2 (62) studies. It is unlikely that our younger patient population accounts for the differences in the observed adverse events. In our study, patients aged 71 and older had an increased risk of hospitalization or ER visits compared with patients aged 25–54.

We also observed the everolimus use decreased in 2015 and 2016, likely due to new alternative treatments approved for mBC. Cyclin-dependent kinase inhibitor palbociclib was approved for treatment for mBC in combination with letrozole in 2015 and in combination with fulvestrant in 2016 [11]. This decrease in claims for everolimus could also be due to a decrease in enrollments in the MarketScan data. In 2015, there was about a 40% decrease in the enrollments in the MarketScan data because they lost two large health plan data contributors in their data [12]. We observed some off-label use of everolimus as we observed claims in 2009–2011, before the drug was FDA approved for mBC in 2012.

As a retrospective claims-based study, our findings should be examined considering a few limitations. Performance status of the patient is an important clinical factor that may impact treatment decisions and outcomes; however, this information was not available. It is possible that some of the ER visits or hospitalizations were due to everolimus toxicity, but given the limitations of the data, causal etiology cannot be established. The results of this study highlight the patient experiences during the treatment in routine practice and thus add to the evidence on real-world use, outcomes, and quality of care. Despite these limitations, our study is the first to evaluate hospitalization and ER visits in a large cohort of patients with mBC treated with everolimus therapy in a real-world clinical practice. Hospitalization and ER visits have critical impact on both economic burden and quality of life, including mobility, functional status, and mental health for patients, and thus it is important to be characterized.

Conclusion

Our results describe patterns of everolimus use and hospitalization or ER visits potentially associated with this treatment. The evaluation of HSP/ER over an 8-year period is another unique feature of our study. As new targeted therapies are incorporated into clinical practice, it is crucial to describe the adverse events associated with them in the general population. This much-needed information will provide providers and patients with accurate data regarding risks and benefits and will help identify patients at higher risk of adverse events to avoid serious complications and facilitate evidence-based decision making.

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Disclosures

Mariana Chavez-MacGregor: Novartis (RF), Roche, Pfizer, Eisai, Abbott (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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