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Effectiveness of Everolimus Versus Endocrine Monotherapy or Chemotherapy Among HR+/HER2− mBC Patients With Multiple Metastatic Sites

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ABSTRACT

Purpose: This review compared the real-world effectiveness of everolimus-based therapy versus endocrine monotherapy or chemotherapy in postmenopausal hormone receptor positive (HR+)/ human epidermal growth factor receptor 2-negative (HER2−) metastatic breast cancer (mBC) patients with multiple metastatic sites.

Methods: This retrospective chart review examined a nationwide sample of postmenopausal HR+/HER2− mBC women with ≥2 non–lymph-node metastatic sites. Patients must have initiated everolimus-based therapy (monotherapy or combination therapy including everolimus), endocrine monotherapy (any endocrine agent), or chemotherapy (monotherapy or combination with another chemotherapeutic or endocrine agent) for mBC between July 1, 2012 and August 15, 2013 after nonsteroidal aromatase inhibitor failure. Progression-free survival and time on treatment were compared using Kaplan-Meier analysis and Cox proportional hazard models, adjusting for line of therapy and baseline characteristics.

Findings: One hundred patients received everolimus-based therapy, 79 received endocrine monotherapy, and 86 received chemotherapy. Everolimus-based therapy was associated with significantly longer progression-free survival and time on treatment than endocrine monotherapy and chemotherapy.

Implications: Among HR+/HER2− mBC patients with multiple metastatic sites, everolimus-based therapy was associated with better real-world effectiveness than endocrine monotherapy or chemotherapy. (*Clin Ther*. 2016;∎:∎∎∎–∎∎∎)

Key words: chemotherapy, clinical outcome, endocrine therapy, everolimus, HR+/HER2− metastatic breast cancer.

INTRODUCTION

Breast cancer (BC) is the most prevalent cancer among women, with an estimated 1.67 million new cases diagnosed annually around the world.[1] In the United States, where BC represents 14% of all new cancer cases, BC will develop in 1 in 8 women in their lifetime.[2,3] Hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2−) is the most common subtype of BC, accounting for ∼70% of all BC cases. It occurs most frequently in postmenopausal women, as the relative incidence of HR overexpression increases with age.[4,5] Among patients with any stage of BC, the 5-year survival rate after diagnosis is 91%, but among patients with metastatic BC (mBC), the 5-year survival rate is only 25%.[2]

Disease prognosis further worsens among mBC patients with multiple metastatic sites. One study of mBC patients showed that having fewer than 2 metastatic sites and the absence of visceral metastases were positive prognostic factors of overall survival. Another study similarly showed that the median overall survival was longer among mBC patients with a single metastatic site compared with those with multiple metastatic sites.[6,7] The findings demonstrate the unmet needs and challenges in treating this patient population with advanced BC.

The National Comprehensive Cancer Network treatment guidelines recommend the use of endocrine therapy as a first-line treatment in overall HR+/HER2− mBC patients.[8] However, resistance to an endocrine therapy eventually develops in most mBC

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patients. In the event of progression or unacceptable toxicity with the current endocrine therapy, the National Comprehensive Cancer Network guidelines recommend initiation of a subsequent line of endocrine therapy as long as there is treatment response with either shrinkage of the tumor or long-term disease stabilization (clinical benefit) with this later line of treatment, for a total of 3 sequential lines of endocrine therapy, including the combined use of endocrine therapy and targeted therapy such as everolimus and palbociclib or until symptomatic visceral disease develops in the patient, at which time chemotherapy is recommended.[8] There are no specific guidelines for the treatment of patients with multiple metastatic sites. In practice, these patients are often treated with chemotherapy in earlier lines, possibly due to the lower effectiveness of endocrine therapy in that setting.[9]

Everolimus, a mammalian target of rapamycin inhibitor, was approved in July 2012 for use in combination with exemestane for the treatment of HR+/HER2− mBC in patients in whom a nonsteroidal aromatase inhibitor failed. The efficacy and safety of everolimus-based therapy have been proven in several clinical trials, including the Phase III BOLERO-2 (Breast Cancer Trials of Oral Everolimus-2) trial and the Phase II TAMRAD (Tamoxifen-RAD001 Versus Tamoxifen Alone in Patients With Anti-aromatase Resistant Breast Cancer) trial.[10,11] For example, in BOLERO-2, the progression-free survival (PFS) interval of patients receiving everolimus/exemestane combination therapy was more than twice as long as that of patients receiving exemestane monotherapy.[10] The comparative efficacy of everolimus-based therapy versus chemotherapy has been examined in a network meta-analysis of mBC clinical trials, showing that the PFS of everolimus/exemestane combination therapy was comparable to or better than that of commonly prescribed chemotherapies.[12] In addition, a subgroup analysis of BOLERO-2 showed that everolimus/exemestane combination therapy had comparable efficacy in patients with multiple metastatic sites compared with overall HR+/HER2− mBC patients; the hazard ratio for PFS among the overall population was 0.38, whereas that for patients with multiple metastatic sites ranged from 0.35 to 0.53 depending on the number of organs involved.[13]

Although mBC patients with multiple metastatic sites represent a group with advanced BC with a substantial unmet need, the literature is scarce regarding the real-world comparative effectiveness of available treatment options, especially with regard to recently developed treatments such as everolimus. Using a nationwide sample of patients with HR+/HER2− mBC whose medical records were retrospectively reviewed by their treating physicians, we previously demonstrated that everolimus-based therapy was associated with significantly longer PFS and time on treatment (TOT) compared with endocrine monotherapy[14] and chemotherapy.[15] Using a subset of patients with multiple metastatic sites from the previous sample, this subgroup analysis seeks to address the existing knowledge gap by comparing patient outcomes (i.e., PFS and TOT) among these more morbid patients treated with everolimus-based therapy, endocrine monotherapy, and chemotherapy. The evidence generated from this study may provide valuable information for real-world treatment decision making in this group with advanced BC.

METHODS

Data Source

The study was based on the same chart review sample that was used to study real-world effectiveness of everolimus-based therapy versus endocrine monotherapy[14] and versus chemotherapy.[15] The data source and collection of chart data have been described previously.[14,15] Briefly, community-based medical oncologists and hematologists from a nationwide online panel in the United States were invited to participate in this chart review. Physicians were eligible to participate if they had treated at least 1 patient who met the study inclusion criteria described in the following. Physicians were asked to identify all patients who met the study inclusion criteria and to subsequently select the first patient whose last name began with a random letter generated by the computer. If they had more than 1 patient whose last name matched that letter, they were asked to select the first patient in alphabetical order, based on their first name; if they did not have a patient whose last name matched that, they were asked to move to the next letter in alphabetical order. Each physician was allowed to contribute up to 10 patient charts. The physicians were then instructed to enter information extracted from each selected patient chart into an electronic case report form accessible through a secure