Review

Progression-free Survival With First-line Endocrine-based Therapies Among Postmenopausal Women With HR+/HER2– Metastatic Breast Cancer: A Network Meta-analysis

Rajeev Ayyagari, PhD[1]; Derek Tang, PhD[2]; Oscar Patterson-Lomba, PhD[1]; Zhou Zhou, MSc[1]; Jipan Xie, PhD[1]; David Chandiwana, MSc[2]; Anand A. Dalal, PhD, MBA[2]; and Polly Ann Niravath, MD[3]

[1]*Analysis Group, Inc, Boston, Massachusetts;* [2]*Novartis Pharmaceuticals Corporation, East Hanover, New Jersey; and* [3]*Methodist Hospital, Houston, Texas*

ABSTRACT

Purpose: The comparative efficacy of endocrine-based therapies (ETs) for hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) metastatic breast cancer (mBC) is not well characterized. This network meta-analysis (NMA) synthesized available evidence on progression-free survival (PFS) with first-line ETs for postmenopausal HR+/HER2– mBC.

Methods: A systematic literature review identified randomized controlled trials of first-line ETs. Pairwise hazard ratios and 95% credible intervals (CrIs) were obtained via a Bayesian NMA model. Subgroup NMAs were conducted among late progressors (disease-free interval ≥12 months from completion of [neo] adjuvant therapy with letrozole or anastrozole at the time of randomization) and de novo patients, defined as patients whose initial BC diagnosis is mBC.

Findings: Five trials and 5 regimens (ribociclib + an aromatase inhibitor [AI] [LEE + AI], palbociclib + AI [Pal + AI], fulvestrant 250 mg + AI [Ful250 + AI], fulvestrant 500 mg [Ful500], and AI) were selected. LEE + AI, Pal + AI, Ful250 + AI, and Ful500 had significantly longer PFS versus AI (95% CrI upper-bound ≤1). LEE + AI had a 30% and 29%, and Pal + AI had a 31% and 30%, reduced hazard of progression or death versus Ful250 + AI and Ful500 (95% CrI upper-bound ≤1), respectively. The probability of being the most efficacious was 46% for LEE + AI and 54% for Pal + AI. In subgroup analyses among late progressors, LEE + AI had a 4% reduced hazard of progression or death versus Pal + AI but was not statistically significant. In the de novo analysis, Pal + AI and LEE + AI had a 29% and 40% reduced hazard of progression or death versus Ful500, respectively, but were not statistically significant. In both subgroup analyses, all therapies had significantly longer PFS compared with AI.

Implications: Pal + AI, LEE + AI, Ful250 + AI, or Ful500 as first-line treatment for HR+/HER2– mBC had longer PFS than AI alone. Given the lack of head-to-head clinical trials comparing the efficacy of recently approved first-line ETs for HR+/HER2– mBC, these results have important clinical implications for the treatment of HR+/HER2– mBC in the first-line setting. (*Clin Ther*. ▮▮▮▮;▮:▮▮▮–▮▮▮) © 2018 Elsevier HS Journals, Inc. All rights reserved.

Key Words: endocrine therapy, HR positive/HER2 negative, metastatic breast cancer, network meta-analysis, progression-free survival, targeted therapy.

INTRODUCTION

Breast cancer (BC) is the most common type of cancer in women worldwide.[1] In the United States (US), >252,000 new cases and 40,000 BC-related deaths are expected in 2017.[2] According to a US study,[3]

Accepted for publication March 7, 2018.
https://doi.org/10.1016/j.clinthera.2018.03.004
0149-2918/$ - see front matter

~70% of all BCs test positive for estrogen or progesterone hormone receptor (HR) and negative for human epidermal growth factor receptor-2 (HER2), referred to as HR+/HER2– BC. The likelihood of being diagnosed with HR+/HER2– BC seems to be positively associated with age, with postmenopausal women at particularly high risk due to hormonal factors.[4,5]

Although 90% to 95% of all BC cases are detected at an early stage, ~30% eventually become metastatic (mBC),[6] resulting in a 5-year survival rate of 26%.[2] Patients with mBC have been shown to have a significantly reduced quality of life compared with the general population, particularly in terms of physical, emotional, and social functioning.[7] As the disease progresses and symptoms worsen, loss of function becomes increasingly debilitating, both physically and emotionally. This scenario translates into a substantial economic burden for both patients and society, as evidenced by the high health care costs associated with BC, which are estimated to represent as much as 20% of the total costs of cancer care in the US.[8]

Targeted therapies (TTs) are poised to revolutionize the treatment of mBC as, in combination with endocrine therapy, they have been shown to inhibit cancer progression while avoiding endocrine resistance and offering manageable safety profiles.[9,10] Indeed, in the case of postmenopausal women with not immediately life-threatening HR+/HER2– mBC, the National Comprehensive Cancer Network treatment guidelines[11] currently recommend the use of endocrine-based therapy (ET). These recommendations include third-generation nonsteroidal aromatase inhibitors (AIs) such as anastrozole and letrozole, the steroidal AI exemestane, and the selective estrogen receptor downregulator fulvestrant[12] with letrozole,[13] and endocrine therapy in combination with TT including everolimus+exemestane,[14] palbociclib + letrozole,[15,16] and ribociclib + letrozole.[19] If ET fails, chemotherapy is recommended when symptomatic visceral disease is present or the cancer is either rapidly progressing or immediately life-threatening.[11] However, chemotherapy is often accompanied by serious adverse events of grade 3/4, further impairing a patient's health-related quality of life.[20]

Head-to-head comparison data on the relative efficacy of first-line therapies for HR+/HER2– BC are lacking. Previous studies have compared these therapies by using network meta-analyses (NMAs).[21–23] However these NMAs were not limited to HR+/HER2– patients and did not account for single lines of therapy, a critical predictor of outcome, but, instead, jointly analyzed first- and second-line settings. Moreover, none of them compared the efficacy of ribociclib versus that of Endocrine-based therapies (either as monotherapy or in combination with TTs or other ETs) in patients with HR+/HER2– mBC in the first-line setting given that the results of the MONALEESA-2 (Mammary Oncology Assessment of LEE011's [Ribociclib's] Efficacy and Safety) trial,[19] which compared ribociclib + letrozole versus placebo + letrozole in previously untreated HR+/HER2– BC, were only recently made available. To fill this knowledge gap, using an NMA, the goal of the present study was to quantitatively synthesize the available evidence on progression-free survival (PFS) associated with endocrine therapies as first-line treatments for HR+/HER2– mBC among postmenopausal women, and evaluate the efficacy of these agents in pre-identified patient populations in an effort to identify subsets of patients most likely to benefit from novel TTs as well as to explore comparative efficacy in more homogeneous settings.

MATERIALS AND METHODS

Systematic Literature Review

A systematic literature review was conducted on June 7, 2016, to identify published randomized controlled trials with efficacy data of endocrine therapy (ie, letrozole, anastrozole, exemestane, tamoxifen, fulvestrant) or TT (ie, palbociclib, everolimus, ribociclib, abemaciclib), either as monotherapy or as part of a combination therapy, for the treatment of women with HR+/HER2– mBC. The search was performed in the following databases: Medline, EMBASE, Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects), and conference proceedings from 2013 to 2016 (American Society for Clinical Oncology, American Association for Cancer Research, American Society for Clinical Oncology Breast Cancer Symposium, San Antonio Breast Cancer Symposium, European CanCer Organisation, European Breast Cancer Conference, and European Society of Medical Oncology). Search terms were constructed for the following 3 domains: (1) disease (ie, mBC); (2) treatments (ie,