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Treatment strategies for advanced hormone receptor-positive and human epidermal growth factor 2-negative breast cancer: the role of treatment order

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ABSTRACT

Although survival rates among patients with breast cancer have improved in recent years, those diagnosed with advanced disease with distant metastasis face a 5-year survival rate of less than 25%, making the management of these patients an area still in significant need of continued research. Selecting the optimal treatment order from among the variety of currently available therapy options presents a relevant challenge for medical oncologists. With the understanding that the majority of patients with breast cancer and those who succumb to this disease have HR-positive disease, this review will focus on treatment options and treatment order in patients with HR-positive advanced breast cancer. While endocrine therapy is considered the preferred treatment for first-line therapy in HR-positive/HER2-negative breast cancer, selection of the specific agent depends on the menopausal status of the patient. Palbociclib, a cyclin-dependent kinase (CDK) 4/6 inhibitor, is also recommended as first-line treatment in patients with ER-positive/HER2-negative disease. In patients with endocrine therapy–resistant disease, specific strategies include sequencing of other antiestrogen receptor agents, or agents that target other molecular pathways. Future treatment strategies for patients with primary or secondary resistance to endocrine therapy for advanced disease are discussed. These strategies include first-line therapy with high-dose fulvestrant or everolimus (in combination with exemestane or letrozole or with other endocrine therapies), use of the PI3K inhibitors (e.g., buparlisib, alpelisib, pictilisib, taselisib), entinostat, CDK 4/6 inhibitors (e.g., palbociclib, ribociclib, abemaciclib), and novel selective estrogen receptor degradation agents that may enhance the targeting of acquired mutations in the *ESR1* gene.

1. Introduction

In the United States, an estimated 231,840 cases of breast cancer in women were diagnosed in 2015, and approximately 40,730 women died of the disease (American Cancer Society, 2015). Despite a long-term trend of decreasing mortality due to breast cancer, the 5-year survival rate for patients diagnosed with stage IV (also known as advanced or metastatic) breast cancer with distant metastasis remains around 26% (National Cancer Institute, 2012). Therefore, even with advances in the diagnosis and management of breast cancer, improvement in clinical outcomes is still needed.

Medical oncologists and patients are today faced with a wide array of treatment options for managing advanced breast cancer; thus, choosing the appropriate treatment for individual patients at different stages can be challenging. Because 68% to 78% of all breast cancer cases are thought to express either estrogen and/or progesterone receptors (Li et al., 2003), clarifying treatment options for hormone receptor–positive (HR-positive)/human epidermal growth factor receptor 2–negative (HER2-negative) breast cancer is an important medical need. This review will examine the treatment options available for patients with HR-positive/HER2-negative breast cancer, with an emphasis on the role of treatment order for optimizing outcomes in patients with metastatic breast cancer.

2. Overview of treatment strategies for advanced HR-positive/HER2-negative breast cancer

Current FDA-approved treatment regimens that utilize endocrine therapy for HR-positive advanced breast cancer are summarized in Table 1 (Novartis Pharmaceuticals Corporation, 2015; AstraZeneca Pharmaceuticals LP, 2007; GTx Inc., 2012; AstraZeneca Pharmaceuticals LP, 2013; Novartis Pharmaceuticals Corporation, 2011; Pharmacia & Upjohn Company, 2013; AstraZeneca Pharmaceuticals LP, 2012; Chlebowski, 2013; Pfizer

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Table 1
Approved therapies for hormone receptor–positive advanced breast cancer.

Agent	FDA approval date	Target	Setting	Sequence
Tamoxifen (AstraZeneca Pharmaceuticals LP, 2007)	1977	SERM	First-line	–
Anastrozole (AstraZeneca Pharmaceuticals LP, 2013)	1995	Nonsteroidal aromatase inhibitor	First-line and second-line	After progression on tamoxifen
Toremifene (GTx Inc., 2012)	1997	SERM	First-line	–
Letrozole (Novartis Pharmaceuticals Corporation, 2011)	1997	Nonsteroidal aromatase inhibitor	First-line and second-line	After antiestrogen therapy
Exemestane (Pharmacia & Upjohn Company, 2013)	1999	Steroidal aromatase inhibitor	First-line and second-line	After progression on tamoxifen
Fulvestrant 250 mg (AstraZeneca Pharmaceuticals LP, 2012)	2002	ER antagonist	Second-line	After antiestrogen therapy
Fulvestrant 500 mg (AstraZeneca Pharmaceuticals LP, 2012)	2010	ER antagonist	Second-line	After antiestrogen therapy
Everolimus + Exemestane (Novartis Pharmaceuticals Corporation, 2015)	2012	mTOR inhibitor	Second-line	After failure of letrozole or anastrozole
Palbociclib (Pfizer Labs, 2015)	2015	CDK 4/6 inhibitor	First line	–

Abbreviations: CDK = cyclin-dependent kinase; ER = estrogen receptor; HR = hormone receptor; mTOR = mammalian target of rapamycin; SERM = selective estrogen receptor modulator.

Labs, 2015). Tamoxifen is a nonsteroidal, selective estrogen receptor (ER) modulator (SERM) that binds to ERs to exert its antitumor activity (AstraZeneca Pharmaceuticals LP, 2007). Toremifene is a SERM that binds to the ER to exert estrogenic effects, antiestrogenic effects, or both; however, in the treatment of breast cancer, it is believed that toremifene competes with estrogen for receptor binding sites in cancer cells, thus blocking the growth-stimulating effects of estrogen in the tumor (GTx Inc., 2012). Anastrozole and letrozole are selective nonsteroidal aromatase inhibitors that suppress estrogen biosynthesis in both peripheral and cancer tissue (AstraZeneca Pharmaceuticals LP, 2013; Novartis Pharmaceuticals Corporation, 2011). Exemestane is an irreversible, steroidal aromatase inhibitor that binds to the active site of the enzyme, hence inducing enzyme inactivation and resulting in significantly lower circulating estrogen levels (Pharmacia & Upjohn Company, 2013). Anastrozole, letrozole, and exemestane are indicated for the first- and second-line treatment of patients with advanced breast cancer (AstraZeneca Pharmaceuticals LP, 2013; Novartis Pharmaceuticals Corporation, 2011; Pharmacia & Upjohn Company, 2013). Recently, palbociclib in combination with letrozole was granted accelerated approval by the FDA for the first-line treatment of ER-positive metastatic breast cancer (Pfizer Labs, 2015). Palbociclib, a selective inhibitor of cyclin-dependent kinase (CDK) 4 and 6, blocks cell cycle progression from G1 into S phase, thereby reducing cancer cell proliferation (Pfizer Labs, 2015). Fulvestrant, an FDA-approved second-line endocrine therapy, has a unique mechanism of action that causes it to bind directly to ERs to prevent dimerization and block the transcription of ER-responsive genes (AstraZeneca Pharmaceuticals LP, 2012; Oakman et al., 2011). Everolimus inhibits the mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/AKT pathway, which reduces cell proliferation and angiogenesis. Everolimus has been evaluated and approved in combination with exemestane for the treatment of HR-positive/HER2-negative advanced breast cancer after failure of letrozole or anastrozole (Novartis Pharmaceuticals Corporation, 2015).

3. First-line treatment

Several issues should be considered when selecting treatment for patients with advanced breast cancer. For the first-line treatment of patients with HR-positive/HER2-negative breast cancer, endocrine therapy is the preferred option due to its noted efficacy and relatively low toxicity compared with cytotoxic chemotherapy (Higgins and Wolff, 2008; National Comprehensive Cancer Network, Inc., 2015). The use of endocrine therapy, however, depends on several variables, including whether the patient is pre- or postmenopausal (Cardoso et al., 2014; Milani et al., 2014).

3.1. Postmenopausal women

3.1.1. Endocrine therapy

The options for endocrine therapy for postmenopausal women include nonsteroidal and steroidal aromatase inhibitors, SERMs, selective estrogen receptor degraders (SERDs), progestins, androgens, and high-dose estrogen (Migliaccio et al., 2015). Postmenopausal women who have not developed tumor relapse from previous endocrine-therapy treatment or who have not received endocrine therapy for more than 1 year may be treated with aromatase inhibitors, SERDs, or SERMs (National Comprehensive Cancer Network, Inc., 2015). Aromatase inhibitors, which act to decrease circulating estrogen levels by interfering with estrogen production in peripheral tissues (Chlebowski, 2013; Osborne and Schiff, 2011), are now considered standard first-line therapy for postmenopausal women with ER-positive breast cancer (Shah and Dickler, 2014). Although the survival benefit of aromatase inhibitors versus tamoxifen has been unclear (Nabholtz et al., 2003; Paridaens et al., 2008; Mouridsen et al., 2003), a Cochrane review demonstrated a small but significant benefit in overall survival (OS) for aromatase inhibitors compared to other endocrine therapies (Gibson et al., 2009). A pooled estimate from 13 trials reporting on 2776 events in 4789 women showed a 10% OS benefit with aromatase inhibitors compared with other therapies, such as