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Long-term management of patients with hormone receptor-positive metastatic breast cancer: Concepts for sequential and combination endocrine-based therapies

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ABSTRACT

Treatment options for hormone receptor-positive (HR-positive) metastatic breast cancer (MBC) continue to increase in parallel with expanding knowledge about the complex biology of breast cancer subtypes and resistance mechanisms to endocrine therapy. For patients with HR-positive MBC, there are now an unprecedented number of endocrine-based treatment options that can improve long-term outcomes, while preserving or optimizing quality of life, and that can be used before selecting more cytotoxic chemotherapeutic regimens. In addition to antiestrogens, steroidal and nonsteroidal aromatase inhibitors, the selective estrogen-receptor degrader, fulvestrant, and new endocrine-based combinations provide significant and clinically meaningful improvements in outcomes in the first line setting and beyond. Also, new clinical scenarios and indications for monotherapy endocrine and targeted therapies continue to be explored. Patients have several therapeutic options when their disease progresses or becomes resistant, although the optimal sequencing of these therapies remains unclear. Ongoing research in the resistant/refractory setting is anticipated to continue improving the outlook for these patients. This review will discuss current and investigational approaches to sequential single-agent endocrine and endocrine-based combination therapy for the long-term management of patients with HR-positive, human epidermal growth factor receptor 2-negative MBC.
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Clinical challenges of hormone receptor-positive metastatic breast cancer

An estimated 250,000 new cases of breast cancer are diagnosed in the United States annually [1], and of these patients, approximately 6% initially present to the clinic with metastatic disease. However, regional variations have been reported where prevalence of de novo metastatic presentation may be as high as 19%, due to factors such as affluence and insurance coverage [2,3]. Among those patients diagnosed with primary breast cancer, 20–50% will develop metastatic disease [4]. Because metastatic breast cancer (MBC) is incurable [5], the goals of treatment tend to be focused on individualizing therapy according to the extent of disease, metastatic sites, tumor biologic features, expected response duration, any general and tumor-related comorbidities or symptoms, patient preferences, and quality of life.

Hormone receptor-positive (HR-positive) breast cancer comprises approximately 75–80% of tumors, which are predominantly estrogen receptor-positive (ER-positive) and, to a lesser extent, progesterone receptor-positive (PgR-positive) [6–8]. Breast cancer is also classified according to expression of the human epidermal growth factor receptor 2 (HER2) oncogene [9,10]. To date, HR and HER2 signatures are important prognostic indicators in breast cancer, and are key determinants of systemic treatment selection [11].

Over the past two decades, several "intrinsic" breast cancer subtypes have been recognized: luminal A, luminal B, HER2-enriched, and basal-like [12–14]. These subtypes differ in their associated mutation patterns, epidemiologic risk factors, prognoses, clinical behavior, and treatment response (Table 1) [7,12,14–17].

Endocrine therapy (ET) remains a foundation of treatment for HR-positive breast cancer in the metastatic setting [18,19]. However, clinical decision-making becomes complicated by the heterogeneity of breast cancer, and rapidly evolving disease classification schemes that include molecular profiles, disease behavior, resistance mechanisms, disease- and patient-specific factors (eg, genetic variables, treatment history, demographics), as well as the consideration of benefit:risk profiles. Clinicians in practice encounter a wide array of clinical presentations, and it can be challenging to determine the best sequence of treatments for an

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Table 1
Summary of disease subtype findings highlighting some of the dominant genomic, clinical, and proteomic features [7].

	Luminal A	Luminal B	Basal-like	HER2E
ER-positive/HER2-negative	87%	82%	10%	20%
HER2-positive	7%	15%	2%	68%
TNBC	2%	1%	80%	9%
p53 pathway	TP53 mut (12%) Gain of MDM2 (14%)	TP53 mut (32%) Gain of MDM2 (31%)	TP53 mut (84%) Gain of MDM2 (14%)	TP53 mut (75%) Gain of MDM2 (30%)
PIK3CA/PTEN pathway	PIK3CA mut (49%) PTEN mut/loss (13%) INPP4B loss (9%)	PIK3CA mut (32%) PTEN mut/loss (24%) INPP4B loss (16%)	PIK3CA mut (7%) PTEN mut/loss (35%) INPP4B loss (30%)	PIK3CA mut (42%) PTEN mut/loss (19%) INPP4B loss (30%)
RBI pathway	Cyclin D1 amp (29%) CDK4 gain (14%) Low expression of CDKN2C High expression of RB1	Cyclin D1 amp (58%) CDK4 gain (25%)	RB1 mut/loss (20%) Cyclin E1 amp (9%) High expression of CDKN2A Low expression of RB1	Cyclin D1 amp (38%) CDK4 gain (24%)
mRNA expression	High ER cluster Low proliferation	Lower ER cluster High proliferation	Basal signature High proliferation	HER2 amplicon signature High proliferation
Copy number	Most diploid Many with quiet genomes 1q, 8q, 8p11 gain 8p, 16q loss 11q13.3 amp (24%)	Most aneuploid Many with focal amps 1q, 8q, 8p11 gain 8p, 16q loss 11q13.3 amp (51%) 8p11.23 amp (28%)	Most aneuploid High genomic instability 1q, 10p gain 8p, 5q loss MYC focal gain (40%)	Most aneuploid High genomic instability 1q, 8q gain 8p loss 17q12 focal ERRB2 amp (71%)
DNA mutations	PIK3CA (49%) TP53 (12%) GATA3 (14%) MAP3K1 (14%)	TP53 (32%) PIK3CA (32%) MAP3K1 (5%)	TP53 (84%) PIK3CA (7%)	TP53 (75%) PIK3CA (42%) PIK3R1 (8%)
DNA methylation		Hyper-methylated phenotype for subset	Hypo-methylated	
Protein expression	High estrogen-signaling High cMYB RPPA reactive subtypes	Less estrogen-signaling High FOXM1 and cMYC RPPA reactive subtypes	High expression of DNA repair proteins, PTEN and INPP4B loss signature (p-AKT)	High protein and phosphoprotein expression of HER1 and HER2

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Percentages are based on 466 tumor overlap list.
Abbreviations: DNA, deoxyribonucleic acid; ER, estrogen receptor; HER2E, human epidermal growth factor receptor 2-enriched; mRNA, messenger ribonucleic acid; TNBC, triple negative breast cancer.

individual patient. Expert guidelines provide evidence-based suggestions based on data from clinical study patient populations, but cannot rapidly assimilate new data to guide individualized treatment.

This narrative evaluates current and investigational approaches to sequential single-agent endocrine and endocrine-based combination therapy for the long-term management of patients with HR-positive MBC, focusing on prolonging time to recurrence or progression, tolerability, and quality of life. Because the treatment of HER2-positive disease introduces a far different range of treatment options, this review is limited to HR-positive/HER2-negative MBC. Clinical studies in postmenopausal women with HR-positive recurrent/advanced breast cancer or MBC are also reviewed (Table 2) [20–36].

Endocrine therapy: Mechanisms of action

Endocrine agents include selective estrogen-receptor modulators (SERMs), aromatase inhibitors (AIs), and a selective estrogen-receptor degrader (SERD). These mechanisms have been reviewed extensively and are only summarized briefly here [37–39].

Selective estrogen-receptor modulators (e.g., tamoxifen) bind competitively to ERs and alter the biologic actions of the receptor complex via conformational changes. These agents can have both agonistic and antagonistic effects [38,39]. Aromatase inhibitors reduce estrogen levels by blocking the conversion of androgens to estrogens by the aromatase enzyme. The third-generation AIs, mainly used in the United States, include the steroidal, irreversible agent, exemestane, that binds irreversibly to aromatase, and the nonsteroidal, reversible inhibitors, letrozole and anastrozole. The only United States Food and Drug Administration (FDA)-approved SERD, fulvestrant, is a pure antiestrogen, without estrogenic (agonist) activity. Fulvestrant binds to the ER and accelerates its degradation. It also inhibits receptor dimerization, which may also decrease estrogen-independent signaling [37–39].

HR-positive MBC: Resistance to endocrine therapies

Endocrine therapies block estrogen-driven tumor growth through a variety of mechanisms, but HR-positive MBC can be either intrinsically resistant to treatment (primary resistance) or may acquire resistance during treatment [40].

Mechanisms of endocrine resistance and therapeutic strategies for overcoming them

The numerous and complex mechanisms underlying primary and acquired resistance have been reviewed in detail elsewhere in the literature [37–47] (Fig. 1) [41]. Known mechanisms include dysregulation of ER pathways, alterations in the cell cycle, molecular changes in response to ET, and crosstalk between the growth

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