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Current Status and Future Perspectives of Endocrine Therapy for Breast Cancer: From Classical Approaches to the Evolution of Precision Systemic Medicine

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Abstract

Hormone receptor-positive breast cancer is the most prevalent molecular subtype of breast cancer. Its therapeutic strategy has progressively evolved from simple endocrine deprivation toward a systematic management model centered on endocrine therapy and integrated with molecularly targeted treatment and dynamic monitoring. This review summarizes the developmental trajectory of endocrine therapy for breast cancer, outlines the classical therapeutic agents and combination strategies used after endocrine resistance, and discusses future directions driven by liquid biopsy, artificial intelligence, and emerging estrogen receptor degradation technologies.

Keywords: breast cancer, endocrine therapy, CDK4/6 inhibitors, resistance, liquid biopsy, precision medicine

1. Introduction: From Empirical Observation to the Era of Precision Medicine

Breast cancer remains one of the most common malignancies among women worldwide. According to the World Health Organization, approximately 2.3 million new cases and 670,000 deaths were recorded globally in 2022. (World Health Organization, 2025) In China, the burden of breast cancer continues to increase, with an overall upward trend in incidence over recent decades, making it a major challenge in cancer prevention and control among women. (Lei S, Zheng R, Zhang S, et al., 2021) Within the current molecular classification framework, hormone receptor-positive/HER2-negative breast cancer accounts for approximately 70% of all breast cancers. Because its biological behavior is closely associated with persistent activation of estrogen signaling, endocrine therapy has long served as the therapeutic cornerstone for this subtype. (Lim E, Metzger-Filho O & Winer EP., 2012)

The history of endocrine therapy for breast cancer dates back to the late nineteenth century. In 1896, Beatson first reported clinical remission in advanced breast cancer following oophorectomy, thereby establishing the

fundamental concept that estrogen-dependent tumors could be treated through hormonal manipulation. (Beatson GT., 1896) In the second half of the twentieth century, the clinical introduction of tamoxifen shifted endocrine treatment from invasive endocrine ablation to long-term pharmacologic intervention and marked a major milestone in modern anti-estrogen therapy. (Jordan VC., 2014)

2. Mechanisms of Action and Clinical Applications of Endocrine Therapeutic Agents

2.1 Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators act by competitively binding to the estrogen receptor and exert mainly antagonistic effects in breast tissue. Representative agents include tamoxifen and toremifene. (Robert NJ., 1996) A patient-level meta-analysis by the Early Breast Cancer Trialists' Collaborative Group demonstrated that approximately 5 years of adjuvant tamoxifen significantly reduced the long-term risks of recurrence and breast cancer-specific mortality in patients with estrogen receptor-positive early breast cancer. (Early Breast Cancer Trialists' Collaborative Group, 2011) Regarding extended therapy, the ATLAS trial showed that prolonging tamoxifen treatment from 5 to 10 years further reduced the risks of late recurrence and breast cancer-related death. (Davies C, Pan H, Godwin J, et al., 2013)

2.2 Aromatase Inhibitors

In postmenopausal women, estrogen is derived predominantly from the peripheral conversion of androgens by aromatase. Aromatase inhibitors markedly reduce circulating estrogen levels by blocking this key enzymatic step. (Geisler J., 2011) The ATAC trial established that anastrozole was superior to tamoxifen as initial adjuvant therapy, providing further improvements in disease-free survival and lowering the risk of recurrence. (Cuzick J, Sestak I, Baum M, et al., 2010) The BIG 1-98 trial further supported the important role of letrozole in the adjuvant treatment of postmenopausal patients with hormone receptor-positive early breast cancer. (Ruhstaller T, Giobbie-Hurder A, Colleoni M, et al., 2019) For patients at higher risk of recurrence, prolonged aromatase inhibitor therapy may confer additional benefit. The MA.17R trial showed that extending adjuvant endocrine therapy to 10 years improved disease-free survival and reduced the incidence of contralateral breast cancer. (Goss PE, Ingle JN, Pritchard KI, et al., 2016)

2.3 Selective Estrogen Receptor Downregulators

Fulvestrant binds to the estrogen receptor and promotes receptor degradation, thereby achieving more complete suppression of ER signaling. (Wardley AM., 2005) The FALCON trial demonstrated that, in endocrine therapy-naïve patients with hormone receptor-positive advanced breast cancer, fulvestrant significantly prolonged progression-free survival compared with anastrozole, with a more pronounced effect observed in patients without visceral metastases. (Robertson JFR, Bondarenko IM, Trishkina E, et al., 2016)

2.4 Ovarian Function Suppression

In premenopausal patients, adequate endocrine efficacy depends on effective suppression of ovarian estrogen production. (Klijn JGM, Blamey RW, Boccardo F, et al., 2001) The SOFT and TEXT trials demonstrated that, in premenopausal patients with hormone receptor-positive early breast cancer at higher risk of recurrence, ovarian function suppression combined with exemestane further improved disease-free survival compared with ovarian function suppression combined with tamoxifen. (Pagani O, Francis PA, Fleming GF, et al., 2020)

2.5 Emerging Endocrine Therapeutic Agents

To overcome the limitations associated with intramuscular administration and pharmacokinetics of fulvestrant, oral selective estrogen receptor degraders have become a major focus of recent drug development. (Bardia A, Kaklamani VG, Neven P, et al., 2024) The phase III EMERALD trial demonstrated that, in patients with ER-positive/HER2-negative advanced breast cancer previously treated with endocrine therapy and largely exposed to CDK4/6 inhibitors, elacestrant significantly improved progression-free survival compared with standard endocrine therapy, with more clearly defined benefit in the ESR1-mutant population. (Bidard FC, Kaklamani VG, Neven P, et al., 2022) Based on these findings, the U.S. Food and Drug Administration approved elacestrant in 2023 for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer. (U.S. Food and Drug Administration, 2023) In addition, next-generation oral ER-targeting agents such as camizestrant and giredestrant remain under phase III clinical investigation, indicating that oral ER-directed treatment is still undergoing rapid development. (Hamilton EP, Jhaveri K, Kuemmel S, et al., 2025) PROTAC-based estrogen

receptor degraders provide a novel technological platform for ER-targeted therapy. Reported in 2025, the VERITAC-2 trial showed that vepdegestrant outperformed fulvestrant in the ESR1-mutant subgroup, supporting the translational potential of ER protein degradation strategies. (Campone M, Neven P, Oliveira M, et al., 2025)

3. Combination Strategies and Novel Agents for Endocrine Resistance

3.1 CDK4/6 Inhibitors

CDK4/6 inhibitors represent one of the most important therapeutic advances in hormone receptor-positive advanced breast cancer over the past decade. (de Melo Gagliato D, Cortes J, Curigliano G, et al., 2020) The MONALEESA-7 trial demonstrated that, in premenopausal or perimenopausal patients with HR-positive/HER2-negative advanced breast cancer, ribociclib combined with endocrine therapy not only significantly prolonged progression-free survival but also yielded a clear overall survival benefit. (Im SA, Lu YS, Bardia A, et al., 2019) In high-risk early-stage disease, the monarchE trial showed that abemaciclib combined with standard adjuvant endocrine therapy improved invasive disease-free survival, thereby establishing its role in the adjuvant treatment of high-risk early HR-positive/HER2-negative breast cancer. (Johnston SRD, Harbeck N, Hegg R, et al., 2023) In addition, studies of abemaciclib in patients with brain metastases demonstrated central nervous system penetration and modest intracranial activity, providing a rationale for systemic treatment exploration in patients with metastases at special anatomical sites. (Tolaney SM, Sahebjam S, Le Rhun E, et al., 2020)

3.2 Inhibitors of the PI3K/AKT/mTOR Pathway

Aberrant activation of the PI3K/AKT/mTOR signaling pathway is one of the major molecular drivers of endocrine resistance. (Razavi P, Dickler MN & Shah PD., 2023) The BOLERO-2 trial showed that everolimus combined with exemestane significantly improved progression-free survival in patients whose disease had progressed after treatment with nonsteroidal aromatase inhibitors. (Piccart M, Hortobagyi GN, Campone M, et al., 2014) In the context of molecularly stratified treatment, the SOLAR-1 trial demonstrated that alpelisib combined with fulvestrant significantly improved progression-free survival in patients with PIK3CA-mutant HR-positive/HER2-negative advanced breast cancer, although toxicities such as hyperglycemia and rash require careful management. (André F, Ciruelos E, Rubovszky G, et al., 2019) The CAPItello-291 trial further showed that capivasertib plus fulvestrant improved progression-free survival in HR-positive/HER2-negative advanced breast cancer, with more pronounced benefit observed in tumors harboring PIK3CA, AKT1, or PTEN alterations. (Turner NC, Oliveira M, Howell SJ, et al., 2023) This regimen received FDA approval in 2023, marking an important step toward routine clinical implementation of AKT pathway-targeted therapy. (U.S. Food and Drug Administration, 2023)

3.3 Epigenetic Therapy

Epigenetic abnormalities are closely linked to ER signaling reprogramming and endocrine resistance. (Garcia-Martinez L, Zhang Y, Nakata Y, et al., 2021) The ACE trial showed that tucidinostat combined with exemestane improved progression-free survival in postmenopausal patients with HR-positive advanced breast cancer, providing clinical support for the use of HDAC inhibitors after endocrine resistance. (Jiang Z, Li W, Hu X, et al., 2019)

3.4 Antibody-Drug Conjugates

With the changing landscape of later-line treatment, antibody-drug conjugates are entering the therapeutic sequence for HR-positive breast cancer. (Bardia A, Hurvitz SA, Tolaney SM, et al., 2021) The DESTINY-Breast04 trial demonstrated that trastuzumab deruxtecan significantly improved progression-free survival and overall survival in patients with HER2-low metastatic breast cancer, the majority of whom had hormone receptor-positive disease. (Modi S, Jacot W, Yamashita T, et al., 2022) The TROPiCS-02 trial showed that sacituzumab govitecan improved progression-free survival and overall survival compared with physician's choice chemotherapy in patients with heavily pretreated HR-positive/HER2-negative metastatic breast cancer. (Rugo HS, Bardia A, Marmé F, et al., 2023)

4. Future Perspectives: Toward Dynamic Monitoring and Precision Decision-Making

ESR1 mutation is one of the key mechanisms underlying acquired endocrine resistance in advanced HR-positive breast cancer, and circulating tumor DNA testing offers a practical, noninvasive tool for its dynamic detection. (Venetis K, Crimini E, Sajjadi E, et al., 2023) The

integration of multi-omic data is reshaping the research paradigm for treatment response prediction in breast cancer. Machine learning models can combine genomic, transcriptomic, tumor microenvironmental, and clinical data to build predictive frameworks for therapeutic response and recurrence risk. (Sammut SJ, Crispin-Ortuzar M, Chin SF, et al., 2022) Beyond ER itself, epigenetic regulation, metabolic reprogramming, and the immune microenvironment are emerging as additional directions for resistance intervention. Strategies involving epigenetic targets such as EZH2 and BET, as well as engineered T-cell therapies and personalized vaccines, remain largely in early-stage development. (Chamorro DF, Parihar A, Fain K, et al., 2023)

5. Conclusion

Endocrine therapy for breast cancer has progressed from early empirical oophorectomy to a systematic and precision-based therapeutic framework encompassing adjuvant treatment for early disease as well as first-line and later-line treatment for advanced disease. Tamoxifen, aromatase inhibitors, fulvestrant, and ovarian function suppression form the classical foundation of endocrine treatment, whereas CDK4/6 inhibitors and PI3K/AKT/mTOR pathway inhibitors have reshaped the therapeutic landscape after endocrine resistance. At the same time, oral SERDs, PROTAC degraders, liquid biopsy, and artificial intelligence-based multi-omic integration are driving the management of HR-positive breast cancer away from fixed sequential treatment patterns and toward dynamic monitoring, molecular stratification, and individualized decision-making. Future research should focus on clarifying the optimal treatment sequence for different molecular subgroups, defining key nodes in resistance evolution, and characterizing long-term real-world benefit, with the goal of prolonging survival while better preserving quality of life.

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