Case Report

Sequential treatment failure in ESR1-mutant breast cancer: A case highlighting therapeutic resistance

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ABSTRACT

We report a case of a 37-year-old female with a known history of diabetes mellitus and hypothyroidism, diagnosed with hormone receptor-positive (HR+) infiltrating mucinous carcinoma of the right breast. The disease initially responded to endocrine therapy but later demonstrated resistance, with progression to widespread metastatic disease including lymph nodes, lungs, pleura, pericardium, bones, and brain. Subsequent molecular profiling revealed an estrogen receptor 1 (ESR1) mutation, prompting a change in treatment to elacestrant. Despite multiple lines of endocrine and targeted therapies (including cyclin-dependent kinase4/6 inhibitors and mammalian target of rapamycin inhibitors), the disease continued to progress, underscoring the aggressive nature of ESR1-mutant HR+ breast cancer and the challenges in its management.

Key words: Cyclin-dependent kinase 4/6 inhibitor, Elacestrant, Endocrine resistance, Estrogen receptor 1 mutation, Fulvestrant, Hormone receptor-positive breast cancer, Mammalian target of rapamycin inhibitor, Metastatic breast cancer, Next-generation sequencing, Oral selective estrogen receptor degrader, Personalized oncology, Therapeutic resistance

Hormone receptor-positive (HR+) breast cancer is typically associated with a more indolent clinical course and good response to endocrine therapy. However, acquired resistance remains a major challenge, particularly in metastatic disease. One important mechanism of resistance is mutation of estrogen receptor 1 (ESR1), the gene encoding the estrogen receptor (ER), which can lead to ligand-independent receptor activation and reduced sensitivity to standard endocrine therapies [1]. Newer agents, especially oral selective estrogen receptor degraders (SERDs) such as elacestrant, have shown promise in overcoming resistance in ESR1-mutant metastatic breast cancer [2].

Here, we present a challenging clinical case of a young patient with ESR1-mutant, endocrine-refractory metastatic breast cancer, highlighting sequential treatment failure despite multiple lines of therapy.

CASE REPORT

A 37-year-old female presented with a progressively enlarging mass in her right breast. She has a past medical history of diabetes mellitus and hypothyroidism. She underwent a modified radical mastectomy with axillary lymph node dissection. Histopathology revealed an infiltrating mucinous carcinoma, grade 3, strongly positive for HRs. She was started on adjuvant endocrine therapy with letrozole and leuprolide (for ovarian suppression).

After 5 years of a disease-free interval, she developed new symptoms of breathlessness. Upon arrival, vitals were stable.

Echocardiography showed a pericardial effusion, and cytology of pericardial fluid confirmed metastatic breast carcinoma. Staging with positron emission tomography-computed tomography (PET-CT) revealed extensive lymphadenopathy (cervical, supraclavicular, mediastinal, and retroperitoneal), pleural effusion, and other sites of disease. An endobronchial ultrasound-guided transbronchial needle aspiration was performed; immunohistochemistry of the sampled tissue was positive for cytokeratin 7, GATA3, and epithelial-cadherin, consistent with breast origin.

Systemic therapy was initiated with palbociclib (a cyclin-dependent kinase [CDK]4/6 inhibitor) plus fulvestrant. A PET-CT after 3 months showed partial metabolic response with reduction in lymph node uptake and resolution of pericardial and pleural

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effusions. However, after 6 months, disease progression recurred: PET-CT showed new and more FDG-avid lesions in the lungs, lymph nodes (axillary, cervical, and retroperitoneal), and skeletal metastases. Due to progression, treatment was switched to everolimus (a mammalian target of rapamycin [mTOR] inhibitor) plus exemestane (an aromatase inhibitor). However, after 3 months, imaging demonstrated further progression: a nodular lesion in the right chest wall (surgical site), increased metabolic activity in the right parotid gland's superficial lobe, and worsening marrow lesions (bilateral iliac bones, sacrum, and lumbar vertebra).

Given the aggressive clinical course, next-generation sequencing (NGS) was performed on the tumor tissue. This revealed a mutation in ESR1, consistent with acquired endocrine resistance. On this basis, she was started on elacestrant, an oral SERD, in an effort to target the mutant. Despite this, a PET-CT done 3 months later revealed ongoing disease progression, including multiple metabolically active lymph nodes (left axillary, cervical, retroperitoneal, etc.) and widespread skeletal lesions.

Clinically, her disease remained refractory with limited symptomatic improvement and continued radiological progression.

DISCUSSION

ESR1 mutations have been identified as a key factor in the development and resistance to treatment of breast cancer, particularly in metastatic HR+ patients. About 1% of initial cancers have an ESR1 mutation. Nevertheless, they are detected in 10–50% of metastatic, endocrine therapy-resistant malignancies, where their incidence rises dramatically. This implies that acquired resistance to endocrine therapy may be mostly caused by these mutations [3,4].

This case underlines several key challenges:

(a) ESR1 mutation and endocrine resistance: ESR1 mutations are one of the principal mechanisms of acquired resistance in HR+ metastatic breast cancer [1]. Such mutations often arise after exposure to aromatase inhibitors, leading to ligand-independent activation of ER and reduced efficacy of traditional endocrine agents.

(b) Limitations of current therapies: Although CDK4/6 inhibitors (e.g., palbociclib) can improve outcomes in HR disease, they may not fully overcome the growth advantage of ESR1-mutant clones [5]. mTOR inhibitors (everolimus) plus endocrine therapy remain a standard option, but resistance frequently emerges. Fulvestrant (an injectable SERD) has limited efficacy in some ESR1-mutant settings; in post-CDK4/6 inhibitor patients, progression-free survival (PFS) with fulvestrant has been modest [6].

(c) Role of elacestrant: Elacestrant is a next-generation oral SERD developed to degrade ER (including mutant forms) and to overcome resistance [7]. In the phase III elacestrant metastatic ER-positive research and learning drug trial, elacestrant demonstrated improved PFS in patients with ESR1-mutant, ER, human epidermal growth factor receptor 2-negative metastatic breast cancer compared to standard-of-care endocrine therapy [8]. However, real-world data show that median time to treatment discontinuation and time to next treatment may be limited (~4–6 months), particularly in patients with prior heavy treatment [2]. Concomitant genomic alterations (e.g., polyclonal ESR1 mutations, phosphatidylinositol 3-kinase (PI3K)-pathway mutations) may further reduce efficacy [2]. Pre-clinical models have also suggested that resistance to elacestrant may be mediated by activation of receptor tyrosine kinases, offering potential avenues for combination therapy [9]. There is emerging evidence of combination therapy, e.g., elacestrant + alpelisib in ESR1 + PIK3CA co-mutated metastatic breast cancer, showing clinical activity in heavily pre-treated patients [10].

(d) Need for personalized and dynamic management: This case demonstrates the necessity of molecular profiling (NGS) upon progression to guide therapy. Given the limited benefit of monotherapy in some cases, combination strategies (e.g., SERD + PI3K inhibitor) deserve consideration, especially when co-mutations are present. Close monitoring and perhaps inclusion in clinical trials could be beneficial, given the aggressive and refractory nature of ESR1-mutant disease.

Key lessons from this case include the importance of early genomic testing using NGS when endocrine resistance is suspected, as it enables timely identification of actionable mutations and guides more rational treatment selection; the need to individualize therapy based on the tumor's mutation profile with consideration of combination treatment strategies to overcome or delay resistance; and the recognition that even newer targeted agents such as elacestrant may fail due to emerging resistance mechanisms, highlighting the urgent need for continued research and development of novel therapeutic approaches in endocrine-resistant breast cancer.

CONCLUSION

This case highlights the complexity and clinical aggressiveness of ESR1-mutant, HR+ metastatic breast cancer, especially in a young patient. Despite sequential use of multiple lines of therapy, including CDK4/6 inhibitors, mTOR inhibition, and a next-generation oral SERD (elacestrant), the disease progressed rapidly.

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