Evolving novel anti-HER2 strategies

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The approval of trastuzumab for use in metastatic breast cancer marked a breakthrough in the understanding of the biology of the disease. However, like most cancer therapies, the disease finds a way to advance despite the treatments developed to eradicate it. Although trastuzumab has had a large effect on the treatment of early and advanced-stage disease, a substantial proportion of patients with HER2-positive breast cancer still progress after receiving the drug. Potential mechanisms of resistance to trastuzumab include bypass mechanisms, mutations of the HER2 target, masking of HER2 proteins, inhibition of insulin-like growth factor, and phosphatase and tensin homologue (PTEN) deficiency. Many therapies are being developed to target these mechanisms in patients with HER2-positive, trastuzumab-resistant breast cancer. Additionally, treatment strategies other than trastuzumab with unique mechanisms of action are being assessed in this specific group of patients. In this review, we discuss the emerging data assessing therapeutic approaches in the management of trastuzumab-resistant HER2-positive disease.

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Introduction

Targeted therapy has been used for more than 100 years in the treatment of breast cancer. In 1896, Beatson reported a treatment response after oopherectomy in a premenopausal patient.[1] After ovarian ablation, other targeted agents were developed, such as tamoxifen and aromatase inhibitors. Trastuzumab, a monoclonal antibody targeting the HER2 protein, was introduced in 1998. Around 25% of patients with breast cancer have HER2-positive disease, with positivity assessed by immunohistochemistry, which detects overexpression of the HER2 protein, or fluorescence in-situ hybridisation, which detects amplification of the *HER2* gene. Patients with 3+ staining from immunohistochemistry (from a possible 1+, 2+, or 3+) and patients with a positive result from in-situ hybridisation are considered to benefit most from trastuzumab.[2] Patients with HER2-positive disease have a higher risk of recurrence and death than those with HER2-negative disease. The approval of trastuzumab broadened the scope of targeted therapy and marked the first of many steps toward improved understanding of the biology of breast cancer.

Mechanism of action of trastuzumab

Trastuzumab is a recombinant, humanised monoclonal antibody directed against the extracellular domain of the HER2 protein, which is expressed on the surface of epithelial cells in many healthy tissues, including the breast.[3] Trastuzumab's mechanisms of action are numerous and complex (figure 1).[3] One mechanism of action is via antibody-dependent cellular cytotoxicity; the activation of natural killer cells initiates lysis of cancer cells that are bound to trastuzumab. Trastuzumab also inhibits the formation of p95, a truncated membrane-bound fragment that results from cleavage of the extracellular domain of HER2 and has in-vitro kinase activity. Additionally, trastuzumab inhibits the phosphoinositide 3-kinase (PI3K) pathway, which is activated by overexpression of HER2. PI3K causes translocation of AKT, resulting in its phosphorylation and activation. Once activated, AKT can phosphorylate many sites, leading to cell proliferation. Activated AKT is negatively regulated by phosphatase and tensin homologue (PTEN). Trastuzumab inhibits the PI3K pathway, reducing PTEN phosphorylation and AKT dephosphorylation, therefore increasing cell death.[4,5] Preclinical studies identified another mechanism of action as the reduction of microvessel density, normalisation of vasculature, or both, which improved tumour response; this occurred only in response to combinations of trastuzumab and chemotherapy.[6–8]

Trastuzumab's many mechanisms of action give rise to various mechanisms of resistance (table 1). Although trastuzumab targets HER2, cross-talk among the other extracellular HER proteins (HER1 and HER3) can result in incomplete inhibition and lateral activation, promoting

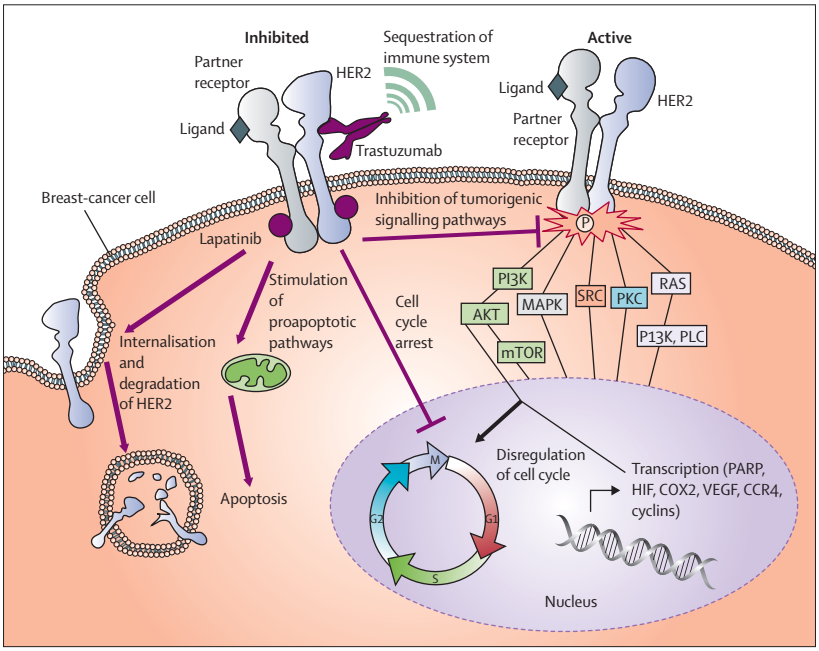

Figure 1: **Mechanism of action of current therapies for HER2-expressing breast cancer**
Constitutively active HER2 receptors on the surface of HER2-expressing breast-cancer cells dimerise with other HER receptors, activating downstream signalling pathways that mediate tumorigenic cell proliferation, survival, and invasion. Trastuzumab prevents constitutive activation of HER2, induces internalisation and degradation of the protein, and stimulates the immune system to recognise HER2-overexpressing cells. Lapatinib binds to HER2 and HER1 and inhibits tumorigenic receptor signalling.

Mechanism of action	Mechanism of resistance
Trastuzumab	
Antibody-dependent cellular cytotoxicity	Mutation in HER2
Cleavage of HER2	Masking of membrane proteins
Inhibition of PI3K pathway	Activation of alternative pathways (bypass mechanism)
Inhibition of angiogenesis	Loss of PTEN
Lapatinib	
Dual TKI of HER1 and HER2	..

PI3K=phosphoinositide 3-kinase. PTEN=phosphatase and tensin homologue. TKI=tyrosine-kinase inhibitor.

Table 1: **Trastuzumab and lapatinib—mechanisms of action and of resistance**

cellular proliferation—ie, the bypass mechanism of resistance.[9,10] Development of a mutation in the HER2 target, leading to trastuzumab failure, is another mode of resistance.[11]

Levels of MUC-4, a membrane-associated mucin, are increased in trastuzumab-resistant cells. MUC-4 can mask the membrane proteins, thus decreasing trastuzumab's ability to bind to the appropriate target.[9] Early progression of HER2-positive breast cancer has been associated with high expression of insulin-like growth factor-1 receptor, and lower response rates have been reported in PTEN-deficient tumours.[4,12,13] These resistance patterns are potential targets for new drug development to overcome trastuzumab resistance.

Downregulation of HER2 expression can occur after treatment with trastuzumab. In the neoadjuvant setting, patients who did not achieve a pathological complete response after trastuzumab were assessed for HER2 status. About a third of the HER2-positive patients who did not achieve a complete response had converted to HER2-negative disease.[14] This result highlights an area of research to better understand trastuzumab resistance and the biology of breast cancer in these particular patients.

Strategies for trastuzumab-resistant disease

Role of trastuzumab after initial progression

In retrospective analyses, continuing trastuzumab alone or in combination with other cytostatic drugs is feasible and safe in patients progressing on trastuzumab therapy. Randomised studies are investigating whether continuing trastuzumab therapy after disease progression (in combination with another chemotherapeutic drug) provides better results than stopping trastuzumab.[15] After 24 weeks, O'Shaughnessy and colleagues[16] found that trastuzumab plus lapatinib significantly improved progression-free survival (12·0 weeks *vs* 8·4 weeks; p=0·029) and clinical benefit rates (25·2% *vs* 13·2%, p=0·020) compared with lapatinib alone in patients who had progressed on prior trastuzumab. Response rates and overall survival were similar.[16] These data show that different mechanisms of action of trastuzumab, such as antibody-dependent cell-mediated cytotoxicity, can be a target to overcome trastuzumab resistance.[17]

New drugs for trastuzumab resistance

Lapatinib is the only therapy other than trastuzumab approved for HER2-positive breast cancer. The US Food and Drug Administration approved lapatinib in 2007 for use in patients with HER2-positive metastatic breast cancer, in whom combined anthracycline, taxane, and trastuzumab therapy had failed. Lapatinib is a small-molecule, dual tyrosine-kinase inhibitor (TKI) of HER1 and HER2.[2] The drug works by competing with ATP for binding sites on intracellular portions of HER1 and HER2, and targets the downstream ERK1–2 pathway, which regulates cell proliferation, and PI3K–AKT, which regulates cell survival. In preclinical trials, lapatinib did not show cross-resistance with trastuzumab, making it a candidate for studies in trastuzumab-resistant breast cancers.[18] Phase 1 data showed responses in heavily pretreated patients with HER1-positive or HER2-positive solid tumours (or both).[19,20] Phase 2 trials showed that lapatinib had efficacy and was well tolerated.[21,22] Response rates as high as 38% were seen when lapatinib was given as first-line therapy in metastatic cancers.[23]

Synergism between lapatinib and capecitabine in early phase 1 trials led to a phase 3 trial in patients with HER2-positive, locally advanced, or metastatic breast cancer refractory to anthracyclines, taxanes, and trastuzumab.[24,25] The study was stopped early when results from a planned interim analysis showed the superiority of the combination therapy.

The combination of lapatinib and trastuzumab was found to be clinically active in a phase 1 dose-escalation study.[26] In a phase 3 trial, progression-free survival and clinical benefit rates were significantly improved by the combination of lapatinib with trastuzumab compared with lapatinib alone.[16] 3000 participants are enrolled in the TEACH (Tykerb Evaluation After Chemotherapy) trial[24] of adjuvant lapatinib therapy, and the global ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization) trial is open for enrolment.[27] Lapatinib is being assessed in the neoadjuvant setting by the CHERLOB (Preoperative Chemotherapy plus Lapatinib or Trastuzumab or Both in HER2-positive Operable Breast Cancer) trial.[28] As additional data become available, the role of lapatinib in different treatment settings (neoadjuvant, adjuvant, and metastatic) will be better defined.

New therapies for metastatic breast cancer

Breast cancer continues to adapt to the treatments available, and clinicians must alter treatment regimens to overcome the disease. Various compounds are being tested to overcome trastuzumab resistance (figure 2). Some of the newer agents are approved for other disease states (TKIs, vascular endothelial growth-factor receptor [VEGFR] inhibitors, and mammalian target of rapamycin [mTOR] inhibitors) or are similar to approved drugs, but are being assessed in the specific population of patients with HER2-positive, trastuzumab-resistant breast cancer (table 2).