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Trastuzumab Resistance: What Are We Offering to Breast Cancer Patients?

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Abstract

Human epidermal growth factor receptor-2 (HER2/ErbB-2) is a receptor tyrosine kinase involved in cell growth and differentiation and over-expressed in about 15-30% of breast cancers. Trastuzumab is an anti-HER2 monoclonal antibody that has significantly improved survival of patients with early and metastatic breast cancer (BC). However, 65% patients experience primary and secondary resistance. This article explores existing and emerging combination therapy for HER2 positive breast cancer, highlighting the success of trastuzumab in combination with another monoclonal antibody, pertuzumab and small molecule tyrosine kinase inhibitors lapatinib and neratinib. Recent studies have indicated that combination of trastuzumab, pertuzumab and lapatinib increases the 3-year overall survival from 90% to 95% in metastatic BC patients. The EPHOS-B trial has shown a remarkable shrinkage of the tumour when lapatinib is used before surgery and chemotherapy. Despite this success, pertuzumab has just been approved for use in the British National Health Service (NHS) while pertuzuamb, lapatinib and neratinib have been approved for European and American markets for a number of years. Lapatinib and neratinib are not available yet in UK. Strict assessment criteria on cost-benefits might limit the access to these drugs to British cancer patients.

Keywords

Breast cancer; Trastuzumab; Resistance; Pertuzumab; Lapatinib; Neratinib; Anti-HER2 monoclonal antibodies; SMTKI

Introduction

Breast cancer (BC) is the second most common cancer in women worldwide [1]. Over-expression of the epidermal growth factor receptor encoded by the HER2/neu gene occurs in 15-25% of all BCs [1]. This phenotype is associated with a faster rate of cancer growth and an increased rate of metastasis, through aberrant signalling activating a variety of survival pathways including PI3K/Akt and RAS/MAPK [1]. The development of trastuzumab (Herceptin®), a humanised monoclonal antibody targeting the extracellular domain of HER2 protein, is one of the most significant advances in breast cancer therapy [1,2] (Figure 1).

Originally approved by the Food and Drug Administration (FDA) in the United States in 1998 for the treatment of metastatic HER2-positive BC, in combination with paclitaxel, trastuzumab recommendation has widened ever since (Table 1). In 2006 FDA approval was expanded to HER2-positive breast cancer patients in combination with chemotherapy and following primary treatment of early stage breast cancer. In 2008 trastuzumab was approved as monotherapy in the adjuvant setting and in 2014 it was approved as first-line treatment in HER2-positive metastatic BC [1,2]. This clearly indicates the clinical benefit of this drug. However, 70% of HER2-positive BC patients do not respond to trastuzumab due to de novo or acquired resistance [2-4]. Current research is focused on understanding mechanisms of trastuzumab resistance to develop new therapeutic strategies.

Mechanisms of resistance to trastuzumab

Several mechanisms of resistance to trastuzumab have been described [2,4] (Figure 2). The extracellular domain of HER2 is proteolytically cleaved by metalloproteinases, thus generating a mutated isoform of HER2, called p95HER2 that cannot bind to trastuzumab (Figure 2). p95HER2 is particularly oncogenic due to its constitutive kinase activation of downstream signaling, thus, inhibiting the effects of trastuzumab [5,6].

Another hypothesised mechanism of trastuzumab resistance is via disruption of the interaction between therapeutic antibodies and target protein. The membrane associated glycoprotein Mucin-4 (MUC4) may mask the extracellular trastuzumab binding domain on HER2 thereby preventing trastuzumab from effectively binding (Figure 2). Nagy et al. used JIMT-1 trastuzumab resistant cell lines to demonstrate that the level of MUC4 is directly related to the ability of trastuzumab to bind, and that reduced levels of MUC4 increased the sensitivity of JIMT-1 cells to trastuzumab, whereas elevated expression of MUC4 masked HER2, resulting in steric hindrance between the drug and target protein [7].

As other members of the HER family are able to mediate oncogenic signalling pathways (PI3K/MAPK), the up-regulation of these proteins may provide a compensatory mechanism for the trastuzumab-mediated inhibition of HER2 [1,2] for example, trastuzumab is unable to prevent HER3 dimerization [8]. Furthermore, HER2-HER3 dimerization results in increased tyrosine phosphorylation of HER3 leading to activation of PI3K pathway (Figure 2) [9]. Likewise ectopic expression of insulin like growth factor 1 receptor (IGF-1R) has been shown to induce resistance to trastuzumab [10]. Deficiency of the phosphatase and tensin homolog (PTEN) deleted from chromosome 10 has also been associated with poor response to trastuzumab [11]. PTEN is a negative regulator of PI3K pathway, and thus, the deficiency of PTEN leads to constitutive activity of PI3K [11,12]. These mechanisms of resistance are currently the subject of intense research, but they have not yet led to a clinical benefit.

Combination regimens

An approach that has been extensively validated in the clinic is the combination of trastuzumab with another fully humanized monoclonal antibody, called pertuzumab, directed against the extracellular domain of HER2 [13]. The two antibodies work synergistically as the differences in their binding sites offer more complete blockade of HER2 (Figure 3). Indeed, upon pertuzumab binding, HER2 cannot dimerize either with another HER2 molecule or

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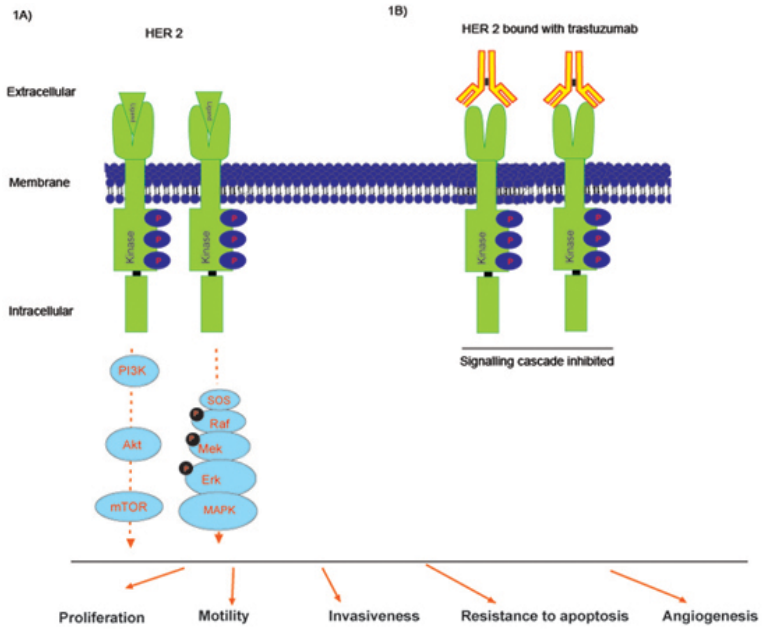
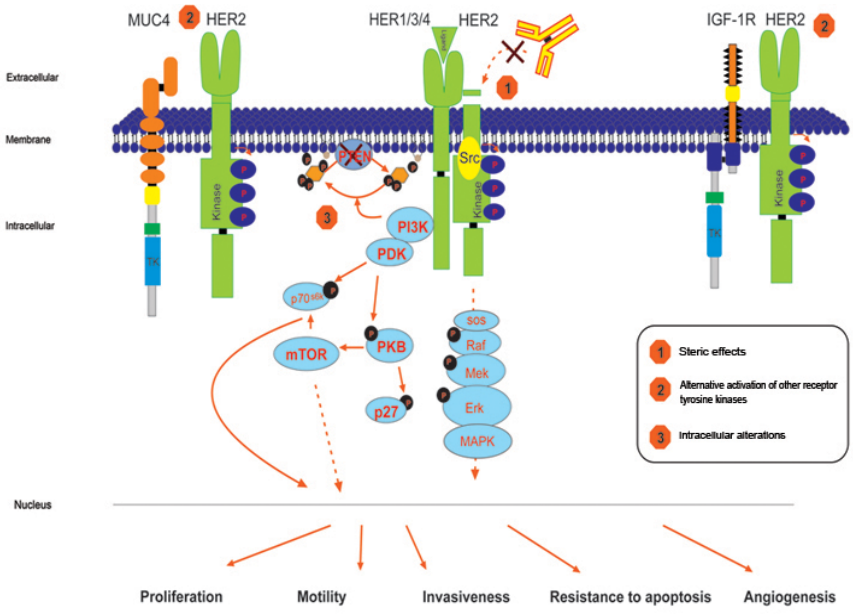


***Note:** A) The HER2 dimerization (extracellular) causes a conformational change to the intracellular tyrosine kinase domain, thus, instigating a kinase cascade via PI3K/Akt and RAS/MAPK . B) Binding of trastuzumab to HER2 homodimers cause inhibition of the signalling cascade.

Figure 1: A schematic representation of the signalling cascade of HER2.



***Note:** Trastuzumab resistance can be achieved through a variety of mechanisms: the presence of MUC4 that masks the trastuzumab binding domain on HER2, the upregulation of HER family receptors to compensate trastuzumab-mediated inhibition of HER2, IGF-1R inducing resistance to trastuzumab and the deficiency of PTEN that leads to constitutive activity of PI3K pathway.

Figure 2: A schematic representations illustrating various mechanisms of trastuzumab resistance.

an alternative HER partner [13]. Thus, the formation of HER2/HER3 dimers, which is the most potent oncogenic receptor pair, is inhibited by pertuzumab [9]. In the neo-adjuvant setting the combination of pertuzumab, trastuzumab and docetaxel was shown to significantly improve pathological complete response (pCR) (45.8%) in early stage BC in comparison to trastuzumab and docetaxel (29%) without substantial differences in tolerability [14].

A more recent study by Swain et al. demonstrated the efficacy of both trastuzumab and pertuzumab in combination with docetaxel [15]. In this trial 808 patients with previously untreated HER2-positive metastatic BC were randomised between two arms, to receive pertuzumab plus the combination of trastuzumab and docetaxel chemotherapy vs. placebo plus the same combination of trastuzumab and docetaxel. Progression free survival (PFS) improved by 6.3

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Table 1: Evolution of drugs approval in UK, EU and US.

Drug	Date of approval UK (NICE)	Date of approval EU (EMA)	Date of approval US (FDA)	Comments
Trastuzamab	March 2002	August 2000	May 1998	Approved for metastatic HER2-positive breast cancer
	August 2006	May 2006	Nov 2006	Approved for adjuvant treatment of early stage, node positive HER2-positive breast cancer, in combination with chemotherapy
	-	-	January 2008	Approved for adjuvant treatment of early stage, node positive or node negative HER2-positive breast cancer
			July 2014	Approved as first line treatment of advanced HER2-positive breast cancer
Pertuzamab	December 2016	March 2013	June 2012	Approval for metastatic HER2-positive breast cancer without prior treatment
		June 2015	September 2013	Accelerated approval in US for use in combination with docetaxel and trastuzamab for HER2-positve early stage, inflammatory or locally advanced breast cancer
Lapatanib	-	June 2008 Conditional marketing authorisation. Full marketing authorisation February 2015	March 2007	Accelerated approval in US for HER2-postive, postmenopausal women with hormone-positive metastatic breast cancer and for whom hormone therapy is indicated in combination therapy for women already using capecitabine.
-		-	January 2010	Accelerated approval in US in combination with letrozole for HER2-postive, postmenopausal women with hormone-positive metastatic breast cancer and for whom hormone therapy is indicated
-	-	Updated approval 2013	-	Updated approval in EU to be used in combination with trastuzumab for HER-2 positive, hormone receptor-negative (HR) metastatic disease that had progressed with prior combination therapy including trastuzumab.
Neratinib	2017 Will report on technology appraisal.	June 2016 Application submitted to EMA	July 2017	Approved in US for extended adjuvant breast cancer that previously has been treated with trastuzamab therapy

NICE - National Institute for Health and Care Excellence

EMA - European Medicines Agency

FDA- Food and Drug Admiration

months in the group treated with pertuzumab combination (PFS=18.7 months) in comparison to placebo (PFS=12.4 months). Moreover, the overall survival (OS) was significantly greater with pertuzumab combination than with the placebo (56.5 vs. 40.8 months). Toxicity was increased in the pertuzumab arm although the quality of life did not differ from the placebo arm [15].

In the phase IV NBRST trial () pertuzumab was administered to HER2 positive BC patients classified based on their molecular subtype (luminal A, luminal B, HER2-enriched and basal-like-and a normal-like subtype), to determine which patients would clinically benefit from dual targeting and whether the HER2-enriched responded better than the others. The results show that the addition of pertuzumab led to an increased pCR rate for all HER2 positive patients except basal-type patients and the effect was most pronounced in the HER2 enriched-type with 75.8% of patients achieving pCR [16].

In 2013, the FDA granted accelerated approval to pertuzumab for use in combination with trastuzumab and docetaxel, as neoadjuvant treatment of patients with HER2-positive breast cancer. This was approved in Europe in 2015 (Table 1).

Another promising strategy to overcome trastuzumab resistance is represented by small molecule dual tyrosine kinase inhibitors (SMDTKI). These molecules are able to compete with adenosine triphosphate (ATP) for the cytoplasmic catalytic kinase domain of HER2, preventing/reducing tyrosine phosphorylation, thus inhibiting downstream signalling [17] (Figure 3). Lapatinib is a reversible SMDTKI, which works by inhibiting the signalling cascade activated by auto-phosphorylation of HER2 homodynes [1,17-21]. Due to its ability to bind to the intracellular domain of HER2, lapatinib is capable of preventing signalling associated with p95HER2 and is suspected to increase trastuzumab-dependent antibody-dependent cell-mediated cytotoxicity (ADCC). Indeed, the accumulation of HER2 on the cell surface increases the overall binding of trastuzumab molecules to HER2 with the effect of attracting more immune cells to the tumour site.

Lapatinib has been successfully combined with a number of chemotherapy drugs including capecitabine [18] and paclitaxel [21]. The combination of paclitaxel and lapatinib versus paclitaxel and placebo has been shown to prolong the median OS from 20.5 months to 27.8 months in metastatic BC patients [21]. Several studies are underway to evaluate the efficacy of the combination of lapatinib with trastuzumab and chemotherapy [19,20,21]. In a phase III study (Trial NCT00281658) in HER2 positive metastatic breast cancer patients, the combination of trastuzumab and lapatinib provided a significant overall survival advantage (4.5 months median), supporting the concept of dual HER2 blockade [19]. Further studies have indicated that combinations of lapatinib with trastuzumab represents a successful approach [21,23]. In the phase III NeoALTTO trial on early HER2 positive BC, the 3-year event-free survival was 76% in the trastuzumab group, 78% in the lapatinib group and 84% in the combination group. The 3-year overall survival was 90% for trastuzumab, 93% for lapatinib and 95% for combination therapy

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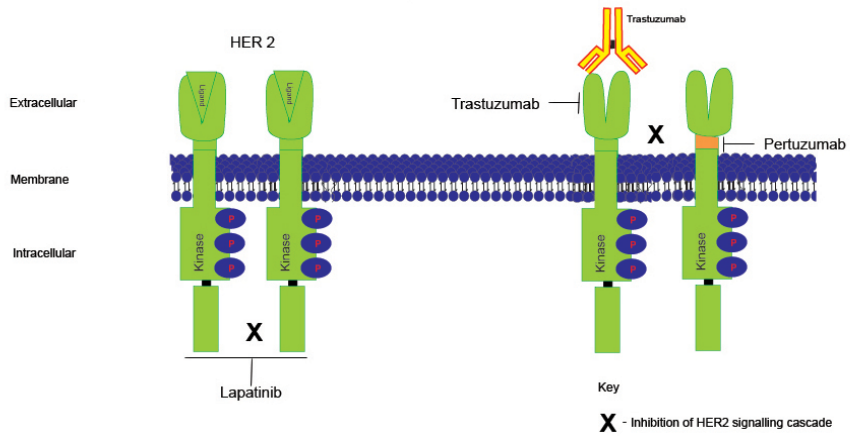

*Note: Trastuzumab and pertuzumab inihibit HER2 homodimerization via binding to HER2 extracellular domain. Lapatinib binds HER2 intracellular domain.

Figure 3: A schematic illustrations of the mechanisms of trastuzumab, pertuzumab and lapatinib.

[22]. Although the overall survival did not significantly differ between the groups, the study confirmed that those who achieved pCR after neoadjuvant therapy experienced longer overall survival than patients that did not reach pCR. In the phase III ALTTO trial, which studied the effects of lapatinib in an adjuvant setting, comparing trasutuzmab mono-therapy, lapatinib mono-therapy and the combination of trastuzumab and lapatinib, the results indicated a 16% reduction in disease-free survival (DFS) in the combination arm compared to trastuzumab alone but was not statistically significant. Moreover, lapatinib was associated with higher rates of toxicity and therefore its role in an adjuvant setting remains uncertain [Piccart-Gebhart, 2016]. A recent meta-analysis which included seven clinical trials concluded that the combination of trastuzumab and lapatinib can improve pCR, PFS and OS without added toxicity in patients with HER2-positive BC. This might indicate that large-scale trials and statistical power are needed to fully evaluate the efficacy of dual blockade regimens [24].

In 2016 at the European Breast Cancer Conference, promising data highlighted the potential of the combination trastuzumab, pertuzumab and lapatinib. The data refer to a clinical trial still on-going, the EPHOS-B, whereby lapatinib, in combination with trastuzumab and pertuzumab, was shown to shrink the tumour size before surgery or chemotherapy in just eleven days. These results indicate that there are patients that might be spared invasive surgery and toxic chemotherapy treatment.

Recently, a phase II study, the PAMELA trial, was conducted on naive HER2 positive BC patients, classified based on their molecular subtype. The patients were treated with lapatinib and trastuzumab and underwent surgery 1-3 weeks after the last dose of treatment. The primary outcome of the study was to assess whether the HER2-enriched subtype predict pCR at the time of surgery. The results showed that 41% of the patients with HER2-enriched subtype achieved pCR whereas only 10% of patients with non-HER2 enriched subtype achieved pCR at the time of surgery [25]. These data suggest that HER2-enriched subtype BC cancer patients are the most likely to benefit from dual blockade regimens.

Lapatinib was approved by the FDA in 2010 in combination with letrozole for the treatment of postmenopausal women with hormone receptor and HER2-positive metastatic breast cancer. Then it was approved in Europe in 2013 to be used in combination with trastuzumab in women with HER2-positive hormone receptor negative metastatic breast cancer that has progressed on prior treatment with trastuzumab in combination with chemotherapy. Lapatinib is not available in the UK on the NHS, the British health service (Table 1).

Recent research has suggested acquired resistance to lapatinib; however this resistance is observed only when lapatinib is used in combination with chemotherapy rather than in combination with trastuzumab and pertuzumab [23]. A proposed mechanism of acquired resistance to lapatinib is thought to be a result of the up-regulation of HER3 receptors. Lapatinib induces activation of the transcription factor FOXO3a, which stimulates the expression of HER3 [26].

As drug resistance is an important feature of reversible SMDTKIs there is a demand for more potent inhibitors, which offer the potential to sustain an antitumor environment. Neratinib is an irreversible pan-HER inhibitor (HER1, 2 and 4) which has shown promising responses in several trials [27]. The FDA recently approved neratinib for early HER2 positive breast cancer based on the data from the pivotal phase III ExteNET trial (FDA.GOV, 2017). In pre-clinical studies neratinib showed better responses than lapatinib, suggesting that neratinib could overcome both primary and acquired resistance to trastuzumab [28]. Neratinib binds to the ATP pocket domain of HER 1, 2 and 4, whereas, lapatanib only targets HER1 and HER2. The additional kinase inhibition may overcome the up regulation of other HER receptor signalling and this may account for the improved responses observed [27]. There are several trials currently underway to evaluate the clinical use of neratinib as treatment for HER2-positive BC: Trial NCT00915018 is comparing neratinib in combination with paclitaxel and trastuzumab against paclitaxel alone in patients with advanced HER2-positive BC. The efficacy of neratinib in comparison to trastuzumab was investigated in a first-line setting together with paclitaxel on recurrent and/or metastatic HER2-positive BC patients. The results showed that the addition of neratinib did not significantly improve the PFS of the patients compared to trastuzumab (12.9 months in both arms) [29].

A study (ExteNET trial) by Chan et al. evaluated the use of neratinib after chemotherapy and trastuzumab based adjuvant therapy in patients with HER2 positive BC. The results indicated that neratinib prolonged the 2-year invasive disease-free survival rate from 91.6% to 93.9%, and reduced the risk of recurrence by 33% [30]. However these results should be considered with caution because of the short follow-up time [30].

In the NSABP-FB-7 study conducted on advanced HER2 positive BC patients, the effects of neratinib and/or trastuzumab plus doxorubicin and cyclophosphamide in a neoadjuvant setting demonstrated a pCR rate of 33% for neratinib, 38% for trastuzumab and 50% in the combination arm. This trial is still on-going.

However, as the tyrosine kinase structure is well preserved, the probability of multiple kinase ligand binding is high due to the non-specific binding properties of small molecule therapies. Thus, more research must be conducted for targeted binding sites in order to produce beneficial outcomes.

Despite the evidence and the results obtained with trastuzumab, pertuzumab, lapatinib and neratinib in clinical trials, British patients seem not to fully benefit from the scientific advancement in the cancer- drug discovery field.

Trastuzumab was approved in the UK in 2002, after pressure from patients, 4 years after its approval in the States. Pertuzumab has just been approved for use in the NHS. In May 2016 NICE, the National Institute for Health and Clinical Excellence, a regulatory body that advises the British health service, did not recommend the use of pertuzumab to treat HER2-positive breast cancer based on the observation that there was uncertainty around how the responses to treatment seen in the clinical trials might translate into long term benefits for patients. The reason for this halt in adopting the new treatment seemed to lay on the ratio between cost and benefits. In November 2016 NICE approved pertuzumab after its manufacturer, Roche, agreed a discount on its price. Lapatinib and neratinib are not available yet in the UK.

Conclusions

The results of the clinical trials presented highlight the efficacy of combining trastuzumab with pertuzumab in breast cancer patients and show promising results when these two are combined with lapatinib. Trastuzumab represents the gold standard for HER2 positive BC. Moreover, molecular subtyping of HER2 positive breast cancer patients has the potential to predict which patients may benefit the most from combinational regimens, to personalize the treatment as well as avoid unnecessary toxicity to those that may not benefit. The personalized treatment based on molecular subtype has not yet entered routine clinical practice. Approximately 11,500 women die every year from breast cancer in the UK and resistance to current treatment is an increasingly important issue. NICE approved pertuzumab for HER2 positive BC only recently after agreeing a discount with Roche. This is also the route followed by other cancer drugs. In July 2016 NICE approved the tyrosine kinase inhibitor bosutinib for chronic myeloid leukaemia patients who have not responded to first and second line treatment by negotiating a discount with the manufacturer of the drug, Pfizer [31]. Prior to this move bosutinib was available to British patients only through the Cancer Drug Fund (CDF) due to its prohibitive price. The CDF was introduced in England in October 2010 to provide access to cancer treatments that are not routinely available on the NHS. After being closed in October 2015, the CDF opened again in April 2016 with 37 indications on its lists. Bosutinib was the first drug on the list to be approved after the reappraisal. Pertuzumab was rejected in May and then approved in November after Roche submitted a further discount. Unfortunately lapatinib and neratinib are not on this list. It is unclear whether they will be approved for the British market.

The British government should take a step forward and negotiate a better price with the pharmaceutical industries [32]. NICE guidelines should be also reviewed in light of new pricing arrangements. It seems a paradox that British residents, that largely fund cancer research through a number of charities sponsoring some of the studies cited in this article, are excluded from the benefits of this research.

We need to rethink how new drugs are made available to patients.

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