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Mechanisms of lapatinib resistance in HER2-driven breast cancer

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ABSTRACT

Targeted therapies have been approved for various malignancies but the acquisition of resistance remains a substantial challenge in the clinical management of advanced cancers. Twenty-five per cent of breast cancers overexpress ErbB2/HER2, which confers a more aggressive phenotype and is associated with a poor prognosis. HER2-targeting therapies (trastuzumab, pertuzumab, TDM1 and lapatinib) are available, but a significant fraction of HER2-positive breast cancers eventually relapse or progress. This suggests that acquired or intrinsic resistance enables escape from HER2 inhibition. This review focuses on mechanisms of intrinsic/acquired resistance to lapatinib identified in preclinical and clinical studies. A better understanding of these mechanisms could lead to novel predictive markers of lapatinib response and to novel therapeutic strategies for breast cancer patients.

Introduction

The relatively new paradigm of "rationally targeted" cancer drug therapies has dramatically impacted the practice of medical oncology. "Personalized" cancer drugs have produced remarkable clinical responses in a subset of patients with advanced systemic disease. This is particularly the case of kinase inhibitors that target the oncogenic forms of epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), breakpoint cluster region/Abelson murine leukemia viral oncogene homolog 1 (BCR/ABL), anaplastic lymphoma kinase (ALK), janus kinase (JAK2) and the BRAF gene [1]. Despite the clinical success, this kind of therapy has a great limitation: a number of patients have intrinsic resistance to these agents, and even responders often develop resistance while in treatment.

The HER2 gene, discovered by Weinberg and associates in 1984 [2], is localized on chromosome17q and encodes a transmembrane receptor tyrosine kinase (RTK) member of ErbB/HER receptor family, which constituted by EGFR/ErbB1, ErbB2/HER2, ErbB3/HER3, and ErbB4/HER4. These receptors are activated by ligand binding to the extracellular domain followed by homo- or heterodimerization and activation of receptors through tyrosine autophosphorylation. HER2 has no known ligands; however, it is the preferential dimerization partner because it displays a high catalytic activity. HER2 signaling is mainly transduced by the phosphatidylinositol 3-kinase (PI3K)/Akt and the Erk1-2/MAPK survival pathways [3]. HER2 is amplified in 25–30% of breast cancers, suggesting that these tumors may be addicted to this oncogene [4]. HER2 overexpression is related to increased aggressiveness, poor prognosis and short survival [5]. The advent of the first HER2-targeted therapy, the humanized monoclonal antibody (mAb) trastuzumab (Herceptin), led to dramatically better outcomes for HER2-positive-breast cancer patients in both the early-stage and metastatic settings [6,7]. More recently, other anti-HER2 drugs have been approved: the humanized monoclonal antibody targeting the HER2 dimerization domain pertuzumab (Perjeta); the dual EGFR/HER2 TK inhibitor (TKI) lapatinib (Tyverb); and the antibody-drug conjugate trastuzumab emtansine (TDM1, Kadcyla).

Among these agents, lapatinib is the only HER2 small molecule TKI approved for breast cancer patients. This dual inhibitor is able to target the TK domains of both, EGFR and HER2, acting as an ATP competitor. The interaction with the receptors prevents the phosphorylation and subsequent signal transduction of the MAPK and the PI3K/Akt pathways, leading to inhibition of cells proliferation and apoptosis induction [8] (Fig. 1). In the clinical setting, the combination of lapatinib and capecitabine is indicated for the treatment of patients with advanced HER2-postive (HER2+) breast cancer in progression after treatment with chemotherapy plus trastuzumab [9]. Combined with paclitaxel, lapatinib is active as first-line treatment [10]. Unfortunately, some patients are constitutively resistant to lapatinib treatment and, even in responders, the disease often progresses because of the selection of tumor cells

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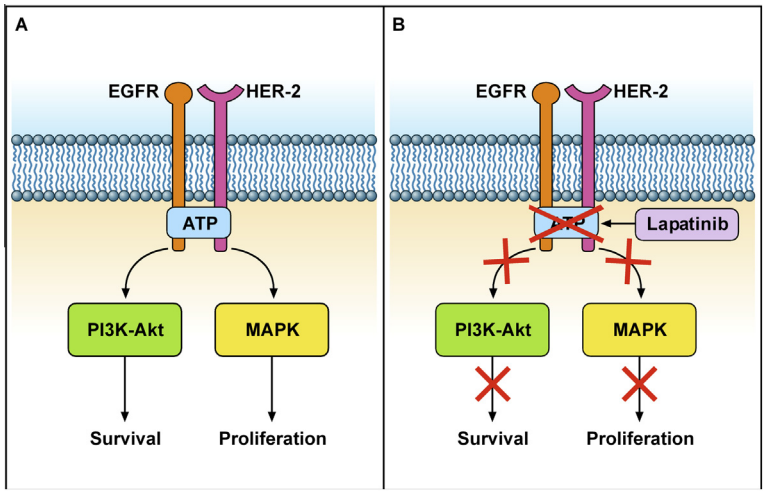

Fig. 1. Lapatinib: mechanism of action. (A) The EGFR ligand induces the formation of the EGFR/HER2 heterodimer and the following ATP-mediated autophosphorylation activates the PI3K/Akt and MAPK pathways. These events lead to cell proliferation and cell survival. (B) Lapatinib, acting as an ATP competitor of both EGFR and HER2, prevents the phosphorylation and subsequent signal transduction of both the MAPK and the PI3K/Akt pathways, thereby leading to inhibition of cell proliferation and apoptosis induction.

Table 1
Mechanisms of resistance to lapatinib.

Mechanism	Factors involved	References
I: Activation of compensatory pathways	(*A*) Receptor tyrosine kinases: HER3, MET, AXL	[13,19,25]
	(*B*) Intracellular kinases: Akt, mTOR, p70S6K, Src, PTK6	[27,29,30,34,36]
	(*C*) Multiple kinases adaptation: JAK, FGFR, DDR1, PIM1, FAK, LIMK	[37,38]
	(*D*) Ligand induced rescue: HRG, NRG1	[40,42]
	(*E*) ER pathway	[45,46]
II: Mutation of the HER2 TK domain	HER2 T798I	[49]
III: Gene amplification	NIBP	[53]

Abbreviations: RTKs: receptor tyrosine kinases; HER: human epidermal growth factor receptor; MET: MET receptor tyrosine kinase; AXL: AXL receptor tyrosine kinase; p70S6K: p70S6 kinase; PTK6: protein tyrosine kinase 6; NRG1: neuregulin-1; HGF: hepatocyte growth factor; HRG: heregulin; ER: estrogen receptor; NIBP: TRAPPC9, trafficking protein particle complex 9.

that have acquired resistance to the drug [11]. Several mechanisms of resistance to lapatinib have been proposed (Table 1, Fig. 2), namely: *I*. activation of compensatory pathways; *II*. mutation of the HER2 TK domain; and *III*. gene amplification. In this review, we describe preclinical and clinical data in order to summarize the main mechanisms of resistance to lapatinib.

Activation of compensatory pathways

Receptor tyrosine kinases

Signaling through other ErbB/HER RTKs can transactivate HER2 and amplify signal transduction downstream, thus bypassing the inhibitory effect of lapatinib. In the context of this receptor network, HER2/HER3 heterodimers are most frequently involved in cancer development and progression [3]. Indeed, the HER3 co-receptor plays an essential role in HER2-mediated transformation, tumor progression and drug resistance. Moreover, upregulation of activated HER3 limits the inhibitory effect of HER TKIs [12]. As demonstrated by Garrett and colleagues, lapatinib-induced HER2 inhibition causes a compensatory PI3K/Akt and FoxO3A-dependent upregulation of HER3 [13]. FoxO3A is a member of FoxO subfamily of forkhead transcription factors, and is regulated by the PI3K/Akt pathway. FoxO proteins have been implicated in the control of genes involved in multiple cellular processes, namely, cell cycle, cell death, neoplastic transformation and epithelial-to-mesenchymal transition [14]. HER2 inhibition by lapatinib is followed by upregulation of HER3 and phospho-HER3. This upregulation depends on activation of the PI3K/Akt pathway and consequent increase of nuclear FoxO3A. Therefore, a combination of HER2-, HER3- and PI3K-targeted agents should be used in patients with HER2-dependent cancers. Moreover, pharmacological inhibition of HER3 sensitizes breast cancer cells to lapatinib, both *in vitro* and *in vivo*, by reducing phospho-HER3, HER3 and phospho-Akt levels [13].

Other RTKs seem to be involved in resistance to lapatinib: among them, c-Met and AXL. The Met TK, also called "hepatocyte growth factor receptor" (HGFR), is a cell surface receptor for HGF (also known as "scatter factor"), whose ligand-induced activation promotes cell proliferation, cell invasion and protection from apoptosis [15]. Compelling evidence implicates HGF/Met signaling in sustaining resistance to targeted therapies. For example, Met has been implicated in trastuzumab resistance [16,17]; it also interacts with HER3 to engage PI3K signaling downstream to EGFR in gefitinib-resistant non-small cell lung cancer [18]. Met can mediate resistance to lapatinib in HER2-amplified gastric cancer cell lines, as recently demonstrated by Chen and colleagues [19]: adding HGF to lapatinib-treated gastric cancer cells induces Met phosphorylation, thereby restoring MAPK and Akt signaling, which mediate escape from lapatinib-induced growth inhibition. Moreover, when gastric cancer cells are treated with a combination of lapatinib and a highly selective Met TKI (PHA-665752), Met-mediated resistance to lapatinib is completely abrogated and growth inhibition restored [19].