

HER-2 Mutations in Non-Small Cell Lung Cancer

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ABSTRACT

Lung cancer is a heterogeneous and complex disease. Oncogenic driver mutations are critical for lung cancer development and serve as therapeutic targets. Oncogenic driver mutations are well defined in epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and reactive oxygen species-1 (ROS-1) mutations. Human epidermal growth factor receptor-2 (HER-2) positivity and anti-HER-2 treatments are well studied in breast cancer. In non-small cell lung cancer (NSCLC), these treatment approaches are under investigation. In NSCLC, mutations of HER-2 are found in 2%–4% of cases. The most commonly encountered mutations are frame insertions in exon 20. There is no evident association between HER-2 amplification and HER-2 mutations. HER-2-targeted therapy needs further clinical investigations in NSCLC.

Keywords: HER-2 mutations, non-small cell lung cancer, HER-2 targeted therapy

ÖZ

Küçük hücreli dışı akciğer kanserinde HER-2 mutasyonları

Akciğer kanseri heterojen ve kompleks bir hastalıktır. Akciğer kanseri gelişimi ve tedavi ajanları için öncü mutasyonlar kritik öneme sahiptir. Öncü mutasyonlar epidermal büyüme faktörü reseptörü (EGFR), anaplastik lenfoma kinaz (ALK) and reaktif oksijen türleri-1 (ROS-1) açısından iyi bir şekilde tanımlanmıştır. İnsan epidermal büyüme faktörü reseptörü-2 (HER-2) pozitifliği ve HER-2'ye yönelik tedaviler meme kanserinde detaylı bir şekilde çalışılmıştır. Küçük hücreli dışı akciğer kanserinde (KHDAK) aynı tedavi yaklaşımları araştırma aşamasındadır. HER-2 mutasyonları küçük hücreli dışı akciğer kanserinde %2-4 oranında görülür. En sık karşılaşılan mutasyon exon 20 insersiyonlarıdır. HER-2 amplifikasyonu ve HER-2 mutasyonları arasında belirgin bir ilişki bulunmamaktadır. Küçük hücreli dışı akciğer kanserinde HER-2 hedefli tedaviler için klinik araştırmalara gereksinim vardır.

Anahtar kelimeler: HER-2 gen mutasyonları, küçük hücreli dışı akciğer kanseri, HER-2 hedefli tedavi

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INTRODUCTION

Lung cancer is the leading cause of cancer-associated death worldwide (1). Lung cancer is traditionally classified as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for approximately 80% of all lung cancers and is further subtyped into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (2). About 57% of patients present with clinically metastatic disease (3), with an overall 5-year survival of 2-4% (4).

Human epidermal growth factor receptor-2 gene (HER-2/ERBB2), which encodes tyrosine kinase, is a member of the ERBB receptor family. The family also includes EGFR (HER1/ERBB1), HER3 (ERBB3), and HER4 (ERBB4). The HER-2 gene, regulated by overexpression and/or gene amplification, is found in many cancers, including breast, stomach, lung, bladder, ovarian, and pancreatic cancer (5). There are three main mechanisms of HER-2 alterations: (1) HER-2 protein overexpression, (2) HER-2 gene amplification, and (3) HER-2 gene mutations (6).

In this review, we will discuss oncogenic driver mutations in HER-2; HER-2 pathway and therapy beyond other driver mutations include EGFR, anaplastic lymphoma kinase (ALK) and reactive oxygen species-1 (ROS-1) mutations.

HER-2 Pathway and HER-2 Mutations

HER-2 is a major proliferative driver that activates downstream signaling through phosphatidylinositol-3-kinases (PI3K)-Protein kinase B (AKT) and methyl ethyl ketone (MEK)-extracellular signal-regulated kinase (ERK) pathways involved with cellular proliferation, differentiation and migration (7). The HER-2 gene is located on chromosome 17. HER-2 has no known ligand; however, it is activated by homodimerization or heterodimerizes with other members of the ERBB family. HER-2 protein overexpression and gene amplification are present in 6-35% and in 10-20% of NSCLC, respectively (8-11). HER-2 protein with strong overexpression (Immunohistochemistry (IHC) score of 3+) is found in only 2-6% of cases (12).

Mutations in HER-2 have been detected in approximately 2-4% of NSCLC. In EGFR/ Kirsten rat sarcoma (KRAS) /ALK

mutation-negative patients, HER-2 mutations can reach up to 6%. This mutation is generally observed in female patients, non-smokers, and patients with adenocarcinoma subtype. These findings are similar to EGFR-mutated NSCLC (13-14). In NSCLC, HER-2 gene mutations occur in exons 18-21 of the tyrosine kinase domain (15). The most commonly encountered mutations are frame insertions in exon 20, but point mutations in exon 20 have also been observed (16,17). HER-2 mutations are leading to constitutive activation of the receptor and downstream AKT and MEK pathways.

There is no gold standard test for detection of HER-2 positivity in NSCLC. The most widely-used tissue-based assays are IHC to quantify the amount of HER-2 protein and fluorescence in situ hybridization (FISH) to identify HER-2 gene copy number. Next generation sequencing (NGS) is a method for identification of HER2 gene mutations in NSCLC (18). HER-2-positive lung cancer does not efficiently define HER-2 status and underestimates the complexity of alterations in this gene.

Anti-HER-2 therapy in NSCLC

In breast and gastric cancer, HER-2 overexpression or gene amplification is associated with sensitivity to HER-2 inhibitors, including trastuzumab, pertuzumab, and lapatinib. However, early trials demonstrated no benefit for trastuzumab in HER-2-amplified NSCLC (19). The addition of trastuzumab to chemotherapy has shown mixed results (20,21). HER-2 amplification has also been described as a mechanism of acquired resistance to EGFR inhibitors. It occurs independently from the T790M mutation (22). Studies investigating trastuzumab and its possible role in NSCLC treatment are gaining interest with the realization that in some patients, lung tumor cells also express the HER-2 mutation (23).

Another treatment strategy for HER-2 mutant patients may be dual EGFR and HER-2 inhibition. Dual inhibition of EGFR and HER-2 has successfully been used in HER-2-positive breast cancer. Afatinib was approved by the Food and Drug Administration (FDA) in July 2013. It is a second-generation tyrosine kinase inhibitor (TKI) that irreversibly binds to both HER-2 and EGFR (24).

Afatinib has shown clinical activity in lung cancer

patients harboring an HER-2 mutation even after failure of other EGFR- or HER-2-targeting therapies (25). The result of afatinib in HER-2-positive NSCLC has been promising. Lapatinib, a dual EGFR and HER-2 inhibitor, is minimally effective as monotherapy for advanced or metastatic NSCLC (26). Neratinib is a pan-HER inhibitor. A phase I study conducted with neratinib and mammalian target of rapamycin (mTOR) inhibitor temsirolimus included five patients with NSCLC and HER-2 mutations evaluable for response. Two had the partial response for approximately 4 and 8 months, respectively, and the other three had stable disease lasting 3 to 5 months (27). Interim analysis of a phase II study (NCT01827267) of HER-2-positive NSCLC showed favorable outcomes with a combination of neratinib plus temsirolimus versus neratinib monotherapy with respect to the response rates and progression-free survival (28). Dacomitinib covalently binds to the adenosine triphosphate domain of each of the three kinase-active members of the HER family: EGFR (HER-1), HER-2, and HER-4. In a phase II trial of patients with advanced NSCLC who failed prior chemotherapy and erlotinib, 1 out of 3 patients with HER2 amplification who received dacomitinib demonstrated a response (29).

The dual HER-2 blockade has shown benefit in HER-2-positive breast cancer. This treatment strategy may be useful but there are no published clinical trials. In HER-2-amplified lung cancer mouse xenograft models, a combination of pertuzumab and ado-trastuzumab showed tumor growth inhibition and superior response to treatment with single agent pertuzumab (30).

CONCLUSIONS

HER-2 positivity and anti-HER-2 treatments are well studied in breast cancer. In NSCLC patients, these treatment approaches are under investigations. In breast cancer, HER-2 amplification occurs in about 20% of patients and is a predictive marker for anti-HER-2 antibodies and TKIs (31-33). In NSCLC, amplification of HER-2 detected by FISH is found in 2%-4% of NSCLC patients. HER-2 aberrations are more prevalent in adenocarcinoma, Asian, non-smoker patients, and HER2 amplification is a negative prognostic marker as shown in a recent meta-analysis (34). Most HER-2 mutations have been described of exon 20 with A775_G776insYVMA. There is no evident association between HER-2 amplification and HER-2 mutations. HER-2 should be used for clinical genotyping of lung cancer. HER-2 mutations in lung cancer can be promising for treatment, just like EGFR, ALK, and ROS-1 mutations. Thus, therapies to be developed against the HER-2 mutation can produce long-term progression and mean survival differences. Patients with HER-2 insertions may benefit from HER-2-targeted therapy, which needs further clinical investigation.

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