Prevalence, Clinicopathologic Associations, and Molecular Spectrum of \textit{ERBB2} (\textit{HER2}) Tyrosine Kinase Mutations in Lung Adenocarcinomas

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Abstract

\textbf{Purpose:} Activating mutations in the tyrosine kinase domain of \textit{HER2} (\textit{ERBB2}) have been described in a subset of lung adenocarcinomas (ADCs) and are mutually exclusive with EGFR and KRAS mutations. The prevalence, clinicopathologic characteristics, prognostic implications, and molecular heterogeneity of \textit{HER2}-mutated lung ADCs are not well established in U.S. patients.

\textbf{Experimental Design:} Lung ADC samples (\(N = 1,478\)) were first screened for mutations in \textit{EGFR} (exons 19 and 21) and \textit{KRAS} (exon 2), and negative cases were then assessed for \textit{HER2} mutations (exons 19–20) using a sizing assay and mass spectrometry. Testing for additional recurrent point mutations in \textit{EGFR}, \textit{KRAS}, \textit{BRAF}, \textit{NRAS}, \textit{PIK3CA}, \textit{MEK1}, and \textit{AKT} was conducted by mass spectrometry. ALK rearrangements and \textit{HER2} amplification were assessed by FISH.

\textbf{Results:} We identified 25 cases with \textit{HER2} mutations, representing 6\% of \textit{EGFR/KRAS/ALK}-negative specimens. Small insertions in exon 20 accounted for 96\% (24/25) of the cases. Compared with insertions in \textit{EGFR} exon 20, there was less variability, with 83\% (20/24) being a 12 bp insertion causing duplication of amino acids YVMA at codon 775. Morphologically, 92\% (23/25) were moderately or poorly differentiated ADC. \textit{HER2} mutation was not associated with concurrent \textit{HER2} amplification in 11 cases tested for both.

\textbf{Conclusions:} \textit{HER2} mutations identify a distinct subset of lung ADCs. Given the high prevalence of lung cancer worldwide and the availability of standard and investigational therapies targeting \textit{HER2}, routine clinical genotyping of lung ADC should include \textit{HER2}. Clin Cancer Res; 18(18); 4910–8. ©2012 AACR.

Introduction

The human epidermal growth factor receptor 2 (\textit{HER2}/\textit{ERBB2}) is a receptor tyrosine kinase of the ERBB family which includes 3 additional members: \textit{EGFR} (\textit{HER1}/\textit{ERBB1}), \textit{HER3} (\textit{ERBB3}), and \textit{HER4} (\textit{ERBB4}). Ligand binding to the extracellular domain of \textit{EGFR}, \textit{HER3}, and \textit{HER4}, results in the formation of catalytically active homo- and heterodimers which, in turn, activate several downstream pathways involved in cellular proliferation, differentiation, migration, and apoptosis (1–3). Despite extensive structural homology with all other members of its family, both along the catalytic intracellular domain and the extracellular putative ligand-binding region, \textit{HER2} has no identified direct ligand. Instead, it functions as the preferred dimerization partner for all other ERBB family receptors (4–6). This observed superior ability for heterodimerization, coupled with a unique basal tyrosine kinase activity, confers to \textit{HER2} a pivotal role in signal transduction with corresponding significant roles in cancer development and progression when its function is deregulated.

Deregulation of the \textit{HER2} gene, through protein overexpression and/or gene amplification, is found in many human cancers most notably breast, ovarian, gastric, and some biologically aggressive forms of uterine carcinomas (7–10). In most cases, overexpression correlates with poor prognosis and, in breast and gastric cancers, it can also predict benefit from \textit{HER2}-targeted therapy. Trastuzumab, a humanized monoclonal antibody targeting the extracellular domain of \textit{HER2}, has shown significant survival advantage in the treatment of \textit{HER2} overexpressing breast cancer (8, 11) when combined with cytotoxic chemotherapy.
ERBB2 (HER2) Mutations in Lung Carcinoma

Translational Relevance
The incidence, clinicopathologic characteristics, and prognostic implications of activating mutations in the tyrosine kinase domain of HER2 in lung adenocarcinomas (ADCs) are not well established.

The current study represents the largest assessment for HER2 mutations \( (N = 1,478) \) in predominantly Caucasian population and the most comprehensive concurrent analysis for other recurrent oncogene mutations. We show that mutations in HER2 identify a distinct subset of lung ADCs with highest prevalence among never-smokers (5%) and which are mutually exclusive with other known driver oncogene mutations, making up 6% of lung ADCs lacking EGFR, KRAS, and ALK alterations. Given the high incidence of lung ADC, it is estimated that there are between 1,000 and 2,000 patients with HER2-mutated lung ADC diagnosed every year in the United States, and their identification would allow for assignment to one of many investigational agents targeting this pathway.

Similar findings have also been recently reported in a phase III study of patients with HER2-positive gastric carcinoma (12). In contrast, whereas overexpression and amplification of HER2 has been reported in up to 1 of 3 of non–small cell lung carcinomas (NSCLCs; refs. 13, 14), statistically significant differences in survival have not been observed (15), and trials exploring the advantage of treatment with trastuzumab have shown only modest or minimal clinical benefits (13, 16).

In 2004, activating mutations within the tyrosine kinase domain of the HER2 gene were discovered in a small subset of NSCLCs (17–22). Their prevalence is reported to be up to 4% (20, 22), and both \textit{in vitro} and \textit{in vivo} studies confirm the oncogenic potential of these mutations (23–25). \textit{In vitro} studies have shown that tumor cells harboring the most prevalent HER2 insertion (YVMA) not only exhibit ligand-independent tyrosine phosphorylation and stronger association with downstream signal transducers that mediate cell survival and proliferative processes, but also potently induce EGFR transphosphorylation, even in the presence of a kinase-dead EGFR (23). Tumor cells harboring HER2 mutations are resistant to EGFR inhibitors but remain sensitive to both HER2 inhibitors and dual EGFR/HER2 inhibitors (25–27).

The most commonly encountered mutations are in-frame insertions in exon 20, but point mutations along the tyrosine kinase domain have also been identified; all are mutually exclusive with common activating mutations in \textit{EGFR} and \textit{KRAS} (17, 20, 28). On the basis of published studies, the clinical and pathologic characteristics of patients with HER2 mutations have been reported to be very similar to those with \textit{EGFR} mutations, being more common in women, Asians, never-smokers, and in adenocarcinoma (compared with squamous carcinoma; ref. 20). To date, however, only a few studies focusing on HER2 mutations have been published (17–22) and most were conducted predominantly in Asian patient populations. The incidence, clinicopathologic characteristics, and prognostic implications of HER2 mutant lung cancer in the U.S. population remain to be more thoroughly defined.

In the current study, we aimed to (i) determine the frequency and spectrum of HER2 mutations in a large cohort of U.S. patients with adenocarcinoma, (ii) assess the clinical and histopathologic characteristics of HER2-mutant tumors, (iii) confirm the mutually exclusive nature of mutations in other genes, including major and minor mutations in \textit{EGFR}, \textit{KRAS}, \textit{BRAF}, \textit{NRAS}, \textit{PIK3CA}, \textit{MEK1}, and \textit{AKT} as well as \textit{ALK} rearrangements, and (iv) compare the survival of patients with HER2-mutant tumors to those harboring other mutually exclusive mutations.

Materials and Methods

Patient selection and mutation analysis
Clinical cases of lung adenocarcinoma received for routine, reflex clinical \textit{EGFR} and \textit{KRAS} testing at Memorial Sloan-Kettering Cancer Center (New York, NY) between January 1, 2009, and December 31, 2010 were selected for the study. Hematoxylin and eosin–stained sections of formalin-fixed paraffin-embedded tissue were reviewed for each sample to identify and circle the areas of highest tumor density. Macrodissection was conducted on corresponding unstained sections to ensure at least 25% tumor content. Genomic DNA was extracted using the DNeasy Tissue kit (Qiagen) following the manufacturer’s standard protocol. Clinical testing for \textit{EGFR} mutations was carried out using fragment analysis for the detection of small indels in exons 19 and 20 and the L858R mutation in exon 21 using previously described methods refs. (29, 30). \textit{KRAS} testing was conducted by a combination of standard sequencing and mass spectrometry genotyping (Sequenom) based on methods previously described (31). As a part of our standard panel of mutation analysis by mass spectrometry, all samples were also concurrently tested for other recurrent point mutations in \textit{EGFR}, \textit{KRAS}, \textit{BRAF}, \textit{NRAS}, \textit{AKT}, \textit{MAPK1}, and \textit{PIK3CA} (Supplementary Table S1; refs. 32, 33). When sufficient tissue was available, samples that were \textit{EGFR}/KRAS wild-type (WT) were tested for \textit{ALK} rearrangements by FISH (Vysis ALK Break Apart FISH Probe Kit) using standard protocols (Supplementary Fig. S1).

HER2 mutation analysis
Cases which were negative for the predominant activating \textit{EGFR} (Exon 19 deletion and L858R) and \textit{KRAS} (G12 and G13) mutations were selected for HER2 testing, given the known mutually exclusive nature of these mutations. HER2 molecular analysis was carried out by 2 methods: a sizing assay to detect small indels in exon 20 and a Sequenom assay panel to detect specific point mutations including L755S, D769H, V777L, and V777M. Testing by fragment analysis followed a protocol similar to \textit{EGFR} testing with fluorescently labeled HER2 primers (29, 30). Briefly, a 300-bp genomic DNA fragment encompassing the entire
coding region of exon 20 was amplified using the primers FW1: 5′-GTTGGGAGGTTGGTCTT-3′ and REV: 5′-Hex - CCT AGC CCC TTG TGG ACA TA - 3′. PCR products were subjected to capillary electrophoresis on an ABI 3730 Genetic Analyzer (Applied Biosystems). Testing for recurrent point mutations was incorporated into the standard Sequenom testing panel with procedures as previously described. All positive cases were confirmed and further characterized by Sanger sequencing using the above primers without fluorescent label.

To confirm the mutually exclusivity of HER2 exon 20 insertions with major EGFR and KRAS mutations, as well as other rarer mutations not well represented in our cohort, we also tested a separate set of adenocarcinomas with a known positive mutation profile and sufficient DNA. Also, to tested a separate set of adenocarcinomas without fluorescent label.

**Analysis of HER2 gene copy number alterations by FISH**

Assessment of HER2 gene copy number was conducted on the same formalin-fixed paraffin-embedded specimens used for DNA extraction. The Vysis PathVysion HER2 DNA Probe Kit (Abbott Laboratories) was used following standard manufacturer’s protocol. At least 40 cells were analyzed for each case by 2 reviewers and were classified according to published criteria (34, 35) as disomy, low polysomy (<4 copies of HER2 in ≤40% of cells), high polysomy (>4 copies of HER2 in >40% of cells), or amplified (HER2/CEP17 ratio per cell ≥ 2, or homogeneously staining regions with ≥15 copies in ≥10% of the cells). Cases with a ratio between 1.8 and 2.2 were reviewed, and wider areas recounted to confirm their status as amplified or not amplified.

**Statistical analysis**

The association between HER2 status and clinical and biologic characteristics was analyzed by Fisher exact test. Age differences were compared using the t test for independent samples. The 2-sided significance level was set at P < 0.05.

Overall survival was calculated using the Kaplan–Meier method. Patients were followed from date of diagnosis of stage IIIb/IV disease to date of death or last follow-up. Survival data were obtained through medical records and the Social Security Death Index and were updated as of November 2011. Group comparisons were conducted using the log-rank test.

**Results**

**Initial screening**

A total of 1,478 ADCs were screened under the clinical assays and Sequenom mass spectrometry–based genotyping assays. Of these, 894 [60%, 95% confidence interval (CI), 58%–63%] were mutation positive (non-HER2) with a distribution as outlined in Supplementary Table S2. Among the remaining 584 "point mutation-negative" samples, 437 were tested by FISH for ALK rearrangements; 36 cases (8%) were positive (36 of 437; 95% CI, 6–11%).

**HER2 mutations**

Five hundred and sixty ADC samples that were negative for the predominant activating EGFR and KRAS mutations were tested for HER2 insertions. This group included 80 cases with point mutations detected by the extended Sequenom panel, 26 cases with ALK rearrangement, and 454 samples with no mutations. Ninety-four cases (out of the above 584 "point mutation-negative" samples) could not be further tested due to insufficient DNA.

Among the 560 ADCs tested, we detected 26 HER2 mutations in 25 cases (5%, 25/560; 95% CI, 3–7%). All mutations were mutually exclusive with point mutations in EGFR, KRAS, BRAF, NRAS, PIK3CA, MEK1, and AKT mutations as well as ALK rearrangements. An additional 53 EGFR and KRAS mutations were detected with Sequenom testing, therefore the HER2 mutation rate among ADC-negative for both major and minor EGFR and KRAS mutations was 5% (26/507; 95% CI, 3%–7%). The incidence among the group negative for EGFR, KRAS, and ALK was 6% (20/335; 95% CI, 3–8%). No HER2 mutations were identified among 104 squamous cell carcinomas and 6 small cell carcinomas tested.

Testing of a separate set of adenocarcinomas with a known positive mutation profile (n = 330, 80 EGFR ex 19 del, 79 L858R, 120 KRAS G12&G13, 7 NRAS, 3 MAPK, 2 AKT, 30 BRAF) confirmed the mutually exclusive nature of HER2 exon 20 insertions with these mutations.

The vast majority of HER2 mutations, 92% (24/26), were in-frame insertions in exon 20, which ranged from 3 to 12 bp, all nested in the most proximal region of the exon, between codons 775 and 881 (Fig. 1). The 12-bp insertion was the most common mutation (83%, 20 of 24) with all cases showing a duplication/insertion of 4 amino acids (YVMA) at codon 775. The 3 bp insertion was the second most common (8%, 2 of 24) and was characterized as a complex insertion-substitution G776 > VC by Sanger sequencing in the 2 identified cases. Two point mutations were also detected, L755S and G776C, corresponding to 8% (2 of 26) of all HER2 mutations identified. The G776C mutation was found concurrently with the HER2 V777_G778insCG (Fig. 3).

**Clinical characteristics of patients with HER2 mutations**

Comparison of HER2 mutants with the HER2 wild-type group. The clinical characteristics of patients with HER2 mutations are summarized in Table 1. After establishing the mutually exclusivity of HER2 mutations with other driver gene mutations, we defined a HER2 WT comparison group by combining all cases confirmed HER2 negative by testing with all cases harboring a mutation in any other gene. This group of 1,359 cases is specified in Table 1 as the HER2 WT group. Comparison with this group shows the patients with HER2 mutations presented at a slightly younger age, with a median age of 64 years versus 66 years. The proportion of
HER2-mutant patients presenting at age 64 or younger (64%) was greater than that of the HER2 WT population (46%, P = 0.04). Significantly, more never-smokers harbored HER2 mutations (5% vs. 1%, P < 0.0001), but there were no significant differences in sex ratios (female 2% vs. male 2%, P = 0.83) or in the stage at presentation. HER2 mutations were not significantly more common among Asian patients (2/61, 3%) vs. Caucasian patients (23/1290, 2%; P = 0.31).

**Comparison of HER2 mutants versus specific molecular subsets.** When the HER2 WT group is stratified into molecular subsets (Table 1), we find that the younger age association is lost with most groups but remains significant only when compared with the cohort with KRAS mutations (P = 0.04). Significant differences were identified in the smoking status of HER2-positive patients when compared with both KRAS and BRAF (P < 0.0001). Similar smoking differences were observed when HER2-mutated patients were compared with the EGFR/KRAS/ALK negative and the negative for all mutations assayed groups (P < 0.0001). In contrast, no significant differences in smoking were identified between the HER2-mutated and the EGFR-mutated groups.

The stratification by molecular subtype also uncovered differences in the stage at presentation of the HER2-mutated group compared with both ALK-rearranged and BRAF-mutated cohorts, the latter 2 being associated with later stage (III–IV) presentation (P = 0.003 and 0.03, respectively).

**Clinical outcomes**

Because of the small sizes of stage- and mutation-specific cohorts, only overall survival was assessed. During follow-up, 468 patients presented with or developed advanced disease (stage IIIb or IV). This included 102 EGFR, 117 KRAS, 28 ALK, 10 BRAF, and 16 HER2 patients. The median follow-up after the diagnosis of advanced disease for all patients was 19 months. The median overall survival by molecular cohort was: HER2 19 months, EGFR 30 months, KRAS 14 months, ALK 25 months, and BRAF 21 months. In this series, the overall survival of the HER2 cohort did not differ significantly from the other molecularly defined cohorts (Fig. 2).
Morphologic spectrum of HER2 mutant lung adenocarcinomas

The vast majority of tumors harboring HER2 mutations (92%, 23/25) were moderate (11) to poorly (12) differentiated and most (80%, 20/25) had high-grade morphology. Eighty-percent (80%, 20/25) were tumors of mixed phenotype with papillary, acinar, solid, and micropapillary components as the most predominant patterns. Three cases had a mucinous component. A bronchoalveolar component was present in 6 tumors, but it was minimal in most cases (67%, 4/6). Only 3 tumors showed a pure phenotype (1 papillary, 1 micropapillary, and 1 solid) but all were small samples and may reflect limited sampling. Two cases were classified as poorly differentiated adenocarcinoma, not otherwise specified because of limited sampling, both with high-grade cytologic features (Fig. 3).

HER2 gene copy alterations by FISH

Analysis for HER2 gene copy number alterations by FISH was conducted on 11 of the 25 HER2 mutated cases based on tissue availability and in 39 HER2 WT cases. None of the mutant cases showed HER2 amplification. Instead, 2 cases (18%) showed high polysomy (>4 copies of both HER2 and CEP17) and 8 (73%) had low polysomy. Among the WT group, one case was amplified (3%, 1/39) with a HER2/CEP17 ratio of 5.9. In this group, 4 cases (10%) had high polysomy and 27 (69%) had low polysomy (Table 2). Of note, the HER2-amplified case was also found to harbor an EGFR exon 19 deletion.

Discussion

The management of lung adenocarcinomas has been transformed in the past decade by the identification of key genetic alterations that activate driver oncogenes. These alterations allow the assignment of patients to targeted treatments based on the specific molecular lesions detected in their tumors.

Mutations in the HER2 gene identify a distinct subset of lung adenocarcinomas. Although less common than EGFR and KRAS, these mutations represent an additional target with already proven sensitivity to HER2 inhibitors in preclinical models (23–25, 36) and anecdotal clinical reports.
(37, 38). Both trastuzumab and lapatinib are available and newer agents, such as dacomitinib and afatinib, are in clinical trials specifically for this indication (36, 39, 40). Given the high prevalence of lung adenocarcinomas, the targeting of these mutations could benefit thousands of patients each year in the United States and elsewhere.

The clinicopathologic characteristics and prognostic implications of HER2-mutated lung adenocarcinoma remain poorly defined. Previous studies report attributes that parallel those seen with EGFR mutations, including associations with female sex, Asian ethnicity, never-smoker status, and adenocarcinoma subtype. Most studies, however, have been conducted in Asia. Only 2 studies have included Caucasian patients, a single study of 157 U.S. patients in whom no mutations were detected (20), and a study of 402 European patients in which a mutation rate of 2% was identified (17). To our knowledge, our study represents the largest assessment for HER2 mutations in a predominantly Caucasian population and the most comprehensive analysis for other mutations in the same cohort.

As HER2 mutations have been previously shown to be mutually exclusive with major mutations in EGFR and KRAS, we selected this negative group as our target for testing, allowing us to enrich for mutant cases. In this subset, we identified 25 HER2-positive cases, all mutually exclusive with other recurrent point mutations in EGFR, KRAS, BRAF, NRAS, PIK3CA, MEK1 and AKT, as well as ALK rearrangements. Additional testing of a separate set of cases known to be positive for major EGFR and KRAS further confirmed the mutually exclusive nature of these mutations. The incidence of HER2 mutations was 5% and 6% among the EGFR/KRAS-negative and the EGFR/KRAS/ALK-negative groups, respectively. On the basis of these mutually exclusive relationships, the proportion of tumors negative for EGFR, KRAS, and ALK, and the prevalence of HER2 mutations in the latter group, we estimate the overall prevalence in the entire group (1,478 patients) to be approximately 2%, which is similar to that observed by Buttita and colleagues (17), in their smaller study of European patients.

Among patients with HER2 mutations, insertions in exon 20 represented the vast majority of the alterations detected (96%, 24/25 patients). As a group, these mutations resemble activating mutations found within exon 20 of EGFR (non-T790M) which have been associated with primary resistance to both first and second generation tyrosine kinase inhibitors (41). In both cases, insertions are in-frame, ranging from 3 to 12 base pairs and confined to a short stretch within the most proximal region of the exon (between the 7th and the 12th codon of the exon). Compared with EGFR, HER2 insertions are less heterogeneous, with over 80% of cases showing the A775_G776insYVMA insertion/duplication (Fig. 4). Two of the mutations...
in our series have not been reported in previous studies (V777_G778insCG and G776C). The significance of the G776C mutation found concurrently with a 6-bp insertion is unknown.

Having confirmed the mutually exclusive nature of HER2 mutations with other driver oncogenes, we then compared the clinical characteristics of HER2-positive patients with the WT group (cases confirmed HER2-negative by testing plus cases with mutations in another gene). In agreement with other groups (17, 20, 42), we found a significant association with never-smoker status (P < 0.0001). In contrast, we did not identify a significant difference by sex or race, although the low number of Asian patients limited the power of this analysis. Patients with HER2 mutations presented at a slightly younger age compared with the overall HER2 WT group and patients with KRAS mutations. While we noted differences in stage at presentation between the HER2 and both the BRAF and ALK subsets, this is difficult to explain biologically and of unclear clinical significance. In this cohort of patients with HER2-mutated lung cancers, survival was numerically similar to other molecularly defined cohorts.

Previous studies have shown that HER2 mutations are confined to the adenocarcinoma subtype of NSCLCs but specific histologic subtype associations have only been assessed by a single group (17). In this study, Buttita et al reported that HER2 mutations are significantly more frequent in ADC with bronchioloalveolar carcinoma features (43). In our study, we do not find this association. Instead we observe significant heterogeneity and a predominance of high grade morphologic features. Most tumors (82%) were of mixed phenotype with papillary, acinar, solid and micropapillary patterns representing the most common components, in decreasing order. The vast majority of tumors (92%) were moderately or poorly differentiated, as also reported in an Asian cohort (28).

In our analyses of HER2 copy number status, we did not find an association of HER2 mutations and gene amplification. While copy number gains were present in most of the cases studied, either as high or low polysomy, this finding was also present among the WT group without significant differences. Although the number of samples studied is small, this suggests that the presence of a HER2 mutation does not necessarily drive copy number gains of the mutated allele. By comparison, a recent study by Li and colleagues reports a significant association with 7 of 8 mutant tumors showing HER2 gains (4 amplification and 3 high polysomy). While copy number variations in their WT group was not reported, previous studies in unselected patients report the presence of HER2 gene amplification by FISH in up to 23% of unselected NSCLC cases (14, 34, 35), suggesting that both amplification and high copy number gains can be present in a significant proportion of cases in the absence of mutations. Although discrepancies could be attributed to the limited number of cases, the combined findings would seem to suggest that, similar to what has been found in EGFR-mutated lung cancer, amplification cannot serve as a surrogate marker for activating HER2 mutations.

In summary, mutations in the tyrosine kinase domain of HER2 identify a distinct subset of lung adenocarcinomas with a higher prevalence among never-smokers. HER2 mutations are mutually exclusive with other activating mutations and independent of HER2 gene amplification. Given the high incidence of lung adenocarcinomas, there may be several thousand patients with this uncommon, yet important, mutation diagnosed every year in the United States, and their identification will allow for assignment to one of many investigational agents targeting this pathway. Testing for activating HER2 kinase domain aberrations, both point mutations and exon 20 insertions, should therefore be incorporated into standard multiplex molecular screening in lung ADC.

Disclosure of Potential Conflicts of Interest

M.G. Kris has a commercial research grant from Pfizer, Inc and Boehringer Ingelheim and is a consultant/advisory board member of Pfizer Inc, Boehringer Ingelheim, and Genentech. No potential conflicts of interest were disclosed by the other authors.
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