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Non-Small Cell Lung Cancer Patients Harboring *HER2* Mutations: Clinical Characteristics and Management in a Real-Life Setting. Cohort *HER2* EXPLORE GFPC 02–14

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ABSTRACT

Background: Mutation of human receptor tyrosine kinase epidermal growth factor receptor-2 (*HER2*) is a rare event, found in approximately 1% non-small cell lung cancers (NSCLC). The objective was to investigate the clinical characteristics and management of *HER2*-mutated NSCLCs in a real-life setting.

Methods: This multicenter study described NSCLCs harboring *HER2* mutations diagnosed between January 2012 and December 2014, according their clinical characteristics,

management, and outcomes: response rate (RR), progression-free survival (PFS), and overall survival (OS).

Results: Thirty patients were included: 66.7% women; median age 65.2 ± 12 years; never or former smokers 73.3%. Of the stage IV patients ($n = 23$), 86% received first-line platin doublet chemotherapy: RR 61.5% and PFS 6.7 (95% CI 5.9–9.5) months; 52.1% received a second-line therapy: RR 18.2% and PFS 4.9 (95% CI 2.5–11.9) months. Median OS of stage IV was 10.7 months and 2-year OS was 27.2% (95% CI 11.7–63.2). All patients with stage I–III NSCLCs were alive at 2 years.

Conclusion: The rarity of *HER2*-mutated NSCLCs requires specific studies.

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Keywords: *HER2* mutation; Lung adenocarcinoma; Management; Prognosis; Target therapy

INTRODUCTION

Human receptor tyrosine kinase epidermal growth-factor receptor-2 (human epidermal growth factor receptor-2; *HER2*) is a membrane-bound ErbB family tyrosine kinase. No ligand has been described for this receptor, which is activated by homodimerization or heterodimerization with other ErbB family members [1–3]. The *HER2* gene has been a recognized proto-oncogene in human cancers for more than two decades. All of the mutations identified were in-frame, 3–12 base-pair insertions into exon 20, leading to constitutive activation of the receptor, and downstream AKT (protein kinase B) and MEK [mitogen-activated protein kinase (MAPK)–extracellular signal-regulated kinase (ERK)] pathways. The *ErbB2* gene, which encodes *HER2*, is a major proliferation driver that activates downstream signaling through phosphoinositide-3-kinase (PI3K)–AKT and MEK–ERK pathways [1–3]. *HER2* mutations satisfy the genetic driver definition and preclinical models proved the concept of the transforming ability of such a genetic alteration. Inducing mutant *HER2* expression in the lung epithelium of mice results in the emergence of invasive adenosquamous carcinomas, with tumor maintenance requiring continuous driver expression, as observed with epidermal growth factor receptor (*EGFR*)-driven cancers [3].

In non-small cell lung cancers (NSCLCs), *HER2* mutation is a rare event [1, 4–7], occurring in approximately 1% of the overall lung cancer population. This rate increases to 4.8% in *EGFR* wild-type lung adenocarcinoma resection specimens [1] and 5.1% in *EGFR*-/*KRAS*- (Kirsten rat sarcoma viral oncogene)/*BRAF*- (v-Raf murine sarcoma viral oncogene homolog B)/*ALK*- (anaplastic lymphoma kinase)/*ROS1* (ROS proto-oncogene-1, receptor tyrosine kinase)-negative patients [8]. The clinical phenotype resembles that of patients with *EGFR*-mutated tumors [9]. *HER2* involvement in lung carcinogenesis has been known for many years but clinical research was slowed by the negative

results obtained with trastuzumab in the first clinical trial. Indeed, adding trastuzumab to gemcitabine–cisplatin or docetaxel failed to show any survival benefit for patients with *HER2* immunohistochemistry (IHC)-positive lung cancers [10].

This retrospective multicenter study was undertaken to improve our understanding of *HER2*-mutated NSCLCs by analyzing the clinical–pathological characteristics of patients with NSCLCs harboring the *HER2* mutation.

METHODS

Physicians at French medical centers were asked to provide retrospectively anonymized data from the medical records of patients at least 18 years old when first diagnosed with *HER2*-mutated NSCLCs between January 2012 and December 2014. *HER2* mutations were identified via one of the following methods: (1) multiplexed sizing assays for insertions and deletions in *EGFR* and *ErB2*; (2) mutational hotspot testing by a mass spectrometry-based nucleic acid assay on the Sequenom™ platform for 91 mutations in six genes (*EGFR*, *HER2*, *KRAS*, *NRAS*, *BRAF*, and *PIK3CA*). Patient demographics and clinical characteristics at NSCLC diagnosis, including age, sex, smoking history (never smoked, current smoker, former smoker), cancer histology, and presence of metastases were collected from patients' charts; treatment information from diagnosis included treatment sequencing and types; clinical outcomes included dates of clinician-defined progression-free survival (PFS) for first-line and second-line treatments based on increased lesion size(s), appearance of new lesions, or clinical worsening and death (if applicable). Overall survival (OS) from diagnosis to death was recorded.

Patient characteristics and treatment information were analyzed descriptively. To evaluate OS, patients were censored at the last follow-up visit. To analyze PFS, patients who died were considered to have progressed. All analyses were computed with SAS v9.3 software (SAS Institute Inc., Cary, NC, USA).

The study was granted the institutional review board (IRB) approval of Saint Etienne (IRBN 102,016/Chuste) and had Comité Indépendant de Traitement des Ressources de Santé (CITRS) authorization (914,146). According to French legislation, information was provided orally to each included patient. The study complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice Guidelines, and local laws. It was also performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

RESULTS

Physicians from 17 medical centers extracted information on 30 NSCLC patients (Table 1). At diagnosis, median age was 65.2 ± 12 years; 66.7% were women; 90% had good performance status (PS 0–1); 30% and 43.3% were never or former smokers, respectively; 93.3% had adenocarcinomas, with 76.7% having advanced disease at diagnosis; 20% had a previous cancer(s) and 8% a family history of cancer. All tumors had an in-frame insertion within the *HER2* gene exon 20 coding sequence. Most of the mutations were exclusive, except for one patient with concomitant *ALK* translocation and another with *RET* (REarranged during

Transfection) translocation. The majority of patients (93.1%) were symptomatic at diagnosis, with the main symptoms being respiratory (77.8%), pain (25.9%), or neurological (11.1%). The most frequent metastatic sites were lung (38.1%), brain (19%), liver (14.3%), and 36.3% had more than two metastatic lesions.

Among the 23 stage IV NSCLC patients, 86% received first-line chemotherapy with platinum-based doublets and bevacizumab (14% received best supportive care); none was prescribed anti-*HER2* therapy. First-line therapy response rate (RR), disease control rate (DCR), and PFS were 61.5%, 84.6%, and 6.7 (95% confidence interval (CI) 5.9–9.5) months, respectively. Progression was characterized by increased sizes of existing lesions (85.7%) and/or appearance of new lesions (64.3%), most often in the lungs (55.6%) or bones (11.1%). New biopsies were obtained from three patients at the first progression but had no impact on NSCLC management. Among the 14 patients who discontinued first-line chemotherapy, 85.7% received second-line therapy, mainly docetaxel, achieving respective RR, DCR, and PFS of 18.2%, 36.4%, and 4.9 (95% CI 2.5–11.9) months. For stage IV patients, 2-year OS was 27.2% (95% CI 11.7–63.2%) and median OS lasted 10.7 months. All seven stage I–III NSCLC patients were alive at 2 years.

DISCUSSION

The clinical and molecular characteristics of *HER2*-mutated NSCLCs included in this study are consistent with other series. As in our cohort, *HER2* mutations appear more common in younger patients, female patients, non-smokers, and adenocarcinomas [8]. In a retrospective study on 64 patients with *HER2*-mutated NSCLCs [11], median age was 62 years, with higher percentages of women (63%) and never smokers (58%); all tumors were adenocarcinomas. In a European cohort [6], median age was 61 years, 62.4% were women, and 60.4% had never smoked. The same characteristics were found in an Asian analysis [8].

Usually, previously described patients had good performance status, allowing a majority to be treated with chemotherapy, 86% herein and

Table 1 *HER2*-mutated NSCLC patient characteristics at diagnosis

Characteristic	All stages (<i>n</i> = 30)	Stage IV (<i>n</i> = 23)
Age (years)	65.2 ± 12	64.4 ± 13
Women	20 (66.7%)	15 (65.2%)
Never	9 (30%)	7 (30.4%)
Former smokers	13 (43.3%)	10 (43.4%)
Performance status 0–1	27 (90%)	19 (82.6%)
Weight loss < 5%	27 (90%)	21 (91.3%)
Caucasian	26 (86.7)	21 (91.3%)
Adenocarcinoma	28 (93.3%)	22 (95.7%)
Symptomatic patients	27 (90)	20 (87%)

79% in the study by Mazières et al. [6]. Chemotherapy responses also seem to have been better than for non-selected NSCLC patients: RR 61.5% and PFS of 6.7 months for our cohort and 43.5% and 6 months, respectively, for the European cohort [6]. A high percentage of patients also received second-line therapy: 85.7% herein and 77% in the European analysis, with PFS exceeding 4 months in both studies. Those results are clearly better than those of patients who received second-line therapy for their NSCLCs without oncogene mutation(s) [11]. This more favorable outcome of patients with *HER2*-mutated NSCLCs, seen herein and as reported by others, might be explained by patient selection, i.e., mainly women and non-smokers, rather than the potential prognostic value of *HER2* mutation. However, in a large cohort analysis [12], median OS (19 months) of the *HER2*-mutated NSCLC patients did not differ significantly from that of other molecularly defined cohorts.

Although *HER2* mutation appears to be an emerging and promising drug-targetable NSCLC marker, the optimal choice of targeted therapy remains poorly defined. Several phase I/II trials [13–15] are investigating the efficacy of irreversible pan-ERBB receptor family inhibitors, such as dacomitinib, neratinib, and pyrotinib. The National Comprehensive Cancer Network (NCCN) recommended trastuzumab or afatinib as potential therapy options for NSCLC patients with *HER2* mutations [16]. In the European cohort, patients treated with *HER2*-targeting agents had a 5.1-month PFS from the start of the first *HER2*-specific treatment. Dacomitinib, an irreversible inhibitor of HER1, HER2, and HER4 tyrosine kinases, achieved partial responses in 12% of patients with *HER2* mutations; afatinib afforded modest responses in 18.2% and median PFS lasted 3.9 months [6].

In a retrospective study [11], 61% of 38 patients received one or more *HER2*-targeted therapies (dacomitinib, afatinib, neratinib, and lapatinib), the median duration of *HER2* tyrosine kinase inhibitors was 2.2 months (28 treatments, range 0.3–16.3 months), and durable clinical benefit of *HER2*-targeted agents was only seen in some patients, including two given dacomitinib for 13 and 17 months, and one prescribed lapatinib for 10 months.

Specific anti-*HER2* treatment outcomes were disappointing in a phase II trial of dacomitinib for patients with *HER2*-mutated lung cancers; none of the 13 patients responded [13]. A recent phase II study investigated pyrotinib, a novel EGFR/*HER2* inhibitor, in heavily pretreated patients with *HER2*-mutated adenocarcinomas obtained promising results: 54.5% (6/11) RR and median PFS lasted 6.2 months [15]. Poziotinib appears also to have some promising activity in this setting in preliminary results [17]. Large cohort studies are still needed to validate pyrotinib efficacy in this setting. The molecular complexities may explain why not all *HER2* mutations or *HER2*-targeting agents are the same and, for reasons not yet discovered, only a subset of such patients responds to various targeted agents. Chemotherapy, particularly pemetrexed doublets, remains the standard of care for these patients.

Our retrospective analysis was conducted to evaluate real-life data for patients with *HER2*-mutated NSCLCs. It has several limitations. First, because it was a retrospective and observational study, collected patient information was not always complete. Although the data reflect clinical practices, it is important to note that, given the study inclusion period, the results cannot be generalized to current practice with more therapeutic options now available. Another limit is that the type of *HER2* mutant variant was not assessed in the majority of cases. However, because of the rarity of *HER2*-mutated NSCLCs and the number of participating centers, we think that this analysis provides valuable real-life information about treatments received and outcomes of patients with *HER2*-mutated NSCLCs.

CONCLUSION

HER2 mutations are rare in NSCLCs and appear to be more common in younger patients, female patients, non-smokers, and adenocarcinoma histology. In these patients, NSCLC responses to platinum chemotherapy seem to have been better than for non-selected NSCLCs and this remains the standard of care as no target therapy has yet achieved satisfactory outcomes.

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Authorship. All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Prior Presentation. Preliminary results of this study were presented in an abstract at the World Conference on Lung Cancer 2016, Vienna.

Disclosures. The Jean-Bernard Auliac, Pascal Dô, Sophie Bayle, Hélène Doubre, Florent Vinas, Jacques Letreut, Lionel Falchero, Pierre-Alexandre Hauss, Pascal Thomas, and Christos Chouaid declare no conflicts of interest with the subject of this manuscript.

Compliance with Ethics Guidelines. The study was granted the IRB approval of Saint Etienne (IRBN 102016/Chuste) and had Comité Indépendant de Traitement des Ressources de Santé (CITRS) authorization (914,146). According to French legislation, information was provided orally to each included patient. The study complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice Guidelines, and local laws. It was also performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. All data generated or analyzed during this study are included in this published article.

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