Outcomes of Pemetrexed-based chemotherapies in HER2-mutant lung cancers

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Abstract

Background: HER2 mutation has been found to be an oncogenic driver gene in non-small cell lung cancers (NSCLC) and HER2-directed therapies have shown promising results in this unique population, while little is known about its association with outcomes of chemotherapy. The aim of this study was to investigate the efficacy of first line chemotherapy in patients with advanced HER2-mutant lung adenocarcinomas.

Methods: Patients with advanced NSCLC (N = 1714) initially underwent testing for EGFR, KRAS, BRAF mutations and ALK, ROS1 rearrangements, and negative cases were then assessed for HER2 mutations using the method of amplification refractory mutation system (ARMS). The efficacy of first line pemetrexed-based chemotherapy was investigated in patients with HER2-mutant and those with EGFR-mutant, ALK/ROS1-rearranged and KRAS-mutant advanced adenocarcinomas.

Results: HER2 mutations were detected in 29 of 572 (5.1%) specimens from a selected population of EGFR/KRAS/BRAF/ALK/ROS1 negative patients. All of them are adenocarcinomas. Among patients with HER2-mutant lung cancers, 25 received pemetrexed-based first line chemotherapy. The objective response rate (ORR) was 36.0%. Their median progression free survival (PFS) was 5.1 months, which was similar with that of KRAS-mutant group (n = 40, 5.0 months, p = 0.971), numerically shorter than that of EGFR-mutant group (n = 74, 6.5 months, p = 0.247) and statistically significantly shorter than that of ALK/ROS1-rearranged group (n = 39, 9.2 months, p = 0.004). Furthermore, HER2 variants subgroup analysis showed that PFS was inferior in A775_G776insYVMA group compared with other variants (4.2 vs 7.2 months, p = 0.085).

Conclusions: Patients with advanced HER2-mutant lung adenocarcinomas showed an inferior outcome of first line pemetrexed-based chemotherapy compared to those with ALK/ROS1 rearrangements, which strengthen the need for effective HER2-targeted drugs in clinical practice.

Keywords: HER2 mutation, Lung adenocarcinoma, Pemetrexed

Background

Human epidermal growth factor receptor2 (HER2) positivity is well-studied in breast cancer, while much less defined in lung cancer. Although anti-HER2 monoclonal antibody such as trastuzumab has been proven effective in breast cancer and gastric cancer [1, 2], the clinical trials [3, 4] of lung cancer including patients treated with trastuzumab combined with chemotherapy failed to demonstrate benefit in survival in HER2 IHC positive patients. Besides that, pan-HER TKI dacomitinib also showed no response in patients with HER2 amplifications in a phase II trial [5].

Apart from HER2 over-expression and amplification, HER2 gene mutation is a distinct entity in lung carcinogenesis with an incidence of 4.8% among EGFR wild-type lung adenocarcinoma resection samples [6]. Drugs that...
target HER2 gene mutations are currently being investigated. The National Comprehensive Cancer Network (NCCN) recommend trastuzumab or afatinib as potential therapy options for non-small cell lung cancers (NSCLC) patients with HER2 mutations. Several phase I/II trials [5, 7–9] is now investigating the efficacy of other irreversible pan-HER receptor family inhibitors, such as dacomitinib, neratinib and pyrotinib. Currently, HER2 mutation is emerging as a promising druggable target, while the optimal choice of targeted therapy remains poorly defined.

Chemotherapy is still the standard first-line regimen for patients with advanced NSCLC who are improper for targeted therapy. Among them, pemetrexed-based regimen has showed superior efficacy with less side effects and was recommended preferentially for patients with adenocarcinomas [10, 11]. ALK/ROS1/RET positive patients showed a superior progression free survival (PFS) after pemetrexed-based therapy than patients with KRAS mutations [12–16]. While the effects of HER2 mutation on the outcomes of pemetrexed-based chemotherapy is still unknown in patients with advanced NSCLC.

Aim to investigate the efficacy of pemetrexed-based chemotherapy in patients with HER2-mutant lung adenocarcinomas, we conducted this retrospective study in Chinese patients with 1714 advanced NSCLC. In addition, we also observed the clinicopathologic and molecular features of HER2 mutations in patients with advanced NSCLC.

Methods
Patients population
Patients with advanced NSCLC (stage IIIB/IV) and performed EGFR, ALK, ROS1, BRAF and KRAS testing at Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China from January 2015 to September 2016 were included into this study. HER2 mutations testing were performed in all these 5 genes pan-negative patients. Their clinical data were collected including age, gender, smoking status, tumor histology, performance status (PS) and the outcomes of anti-cancer therapies. Patients with HER2, EGFR or KRAS mutation or ALK or ROS1 rearrangement and received first-line pemetrexed-based chemotherapy (pemetrexed monotherapy or combination therapy with platinum) were eligible for analysis. A history of radiotherapy, first-line targeted therapy, or immune-directed therapy was exclusionary.

Molecular testing
HER2 mutation testing was performed using the method of amplification refractory mutation system (ARMS) by ADx HER2 Mutation Detection Kit (Amoy Diagnostics, Xiamen, China). Samples positive for HER2 mutations were confirmed by DNA sequencing using primers with the following sequences: 5’GCC ATG GCT GTG GTT TGT GAT AGG3’ (forward) and 5’ATC CTA GCC CCT TGT GGA CAT AGG3’ which amplified a 342-bp fragment in exon20 of the HER2 gene. The details can be referred to our previous study [6].

Similarly, EGFR, BRAF and KRAS mutation were performed using EGFR, BRAF V600 and KRAS Mutations Detection Kit (Amoy Diagnostics, Xiamen, China) respectively by ARMS method. ALK and ROS1 rearrangement testing were performed using AmoyDx EML4-ALK and ROS1 Fusions Detection Kit (Amoy Diagnostics, Xiamen, China) respectively by the method of reverse transcriptase polymerase chain reaction (RT-PCR). The details were described in our previous articles [13, 17–19].

Statistical analysis
Tumor response was evaluated every 2 cycles of chemotherapy according to response evaluation criteria in solid tumors (version 1.1). PFS was defined as the time interval from the first day of treatment to documented disease progression or death of any cause. All of the statistical tests were performed using the SPSS 19.0. Chi-square test or Fisher's exact test was used to examine the clinicopathologic association of HER2 mutations and response rate comparison. Age differences were compared using the t test for independent samples or the one-way analysis of variance. The Kaplan–Meier method was used to estimate the PFS and the log-rank test was used to analyze PFS between the different groups. Results were considered significantly different if the p value was less than 0.05 in a two-way analysis.

Results
Patients’ characteristics
From January 2015 to September 2016, a total of 1714 patients with advanced NSCLC underwent testing for EGFR, KRAS, BRAF, ALK and ROS1. The results showed that there were 809 patients (47.2%) with EGFR mutations, 149 (7.8%) with KRAS mutations, 19 (1.1%) with BRAF mutations, 106 (6.2%) with ALK rearrangements, 43 (2.5%) with ROS1 rearrangements, and 16 patients (0.9%) with multiple positive results. In addition, 572 pan-negative patients also have tested their HER2 status by ARMS and 29 (29/572, 5.1%) were identified as HER2 mutation positive (Fig 1).

HER2-mutant lung cancer patients had a median age of 58 (range 44–77 years) and mutations were more common in females (p<0.001), non-smokers (p = 0.034) and adenocarcinomas (p = 0.002) (Table 1). Twenty-four of 29 patients had available samples for sequencing and had the details variants of HER2 mutation including 14 with exon20 A775_G776insYVMA, 3 with P780_Y781insGSP, 3 with G776 > VC, 2 with G776 > IC, 1 with G776 > LC, and 1 with G776C (Additional file 1: Figure S1).
Outcomes of chemotherapy: Comparison among oncogenic mutations groups

Patients received first-line pemetrexed-based chemotherapy were eligible for analysis (n = 25,144 combined with carboplatin, 7 combined with cisplatin and 4 monotherapy). Since most patients with druggable mutations chose TKI as a first-line treatment, only 74 of 809 EGFR-mutant patients and 39 of 149 ALK/ROS1-rearranged patients were included. While there were a relatively large number of patients with KRAS mutation, the first 40 of KRAS identified were selected for this study.

The baseline characteristics of patients with HER2-mutant were compared with patients with EGFR-mutant, ALK/ROS1-rearranged, and KRAS-mutant lung cancers as summarized in Table 2. HER2, EGFR, KRAS mutations and ALK, ROS1 rearrangements did not co-occur with each other in individual patient samples. KRAS mutations were more frequently detected in patients with more than 65 years old, male and smokers. And comparison revealed no significant differences in terms of PS score (p = 0.269), monotherapy versus combination therapy (p = 0.570), maintenance therapy versus non-maintenance therapy (p = 0.175).

The response was evaluated in all 178 patients. Both the objective response rate (ORR) and the disease control rate (DCR) were not significantly different among four groups (Table 3). However, PFS was significantly different among all groups. Patients in the HER2-mutant group had a median PFS of 5.1 months (95% confidence interval [CI], 4.90–5.30) (95% CI 4.90–5.30), which was numerically shorter than that of the EGFR-mutant group (6.5 months, 95% CI 4.48–8.52, p = 0.247) and significantly shorter than that of the ALK/ROS1-rearranged (9.2 months, 95% CI 6.41–11.99, p = 0.004). Similarly, in KRAS-mutant lung cancers, PFS (5.0 months, 95% CI 3.67–6.33) was inferior compared with EGFR-mutant (6.5 months, p = 0.242) and ALK/ROS1-rearranged (9.2 months, p = 0.007) lung cancers. PFS was not significantly different between the HER2-mutant and the KRAS-mutant lung cancers groups (5.1 vs 5.0 months, p = 0.971) (Fig. 2a).

Outcomes of chemotherapy: Comparison among HER2 variants subgroups

Twenty patients of the 25 patients receiving first-line pemetrexed-based chemotherapy had known HER2 variants (Additional file 1: Figure S1). According to the frequency of the variants, they were divided into the

| Clinical characteristics | Total (n = 572) | HER2 negative (n = 543) | HER2 positive (n = 29) | P value |
|--------------------------|----------------|------------------------|------------------------|---------|
| Age, years (median, range) |                |                        |                        |         |
| < 65                     | 305(53.3%)     | 283(52.1%)             | 22(75.9%)              | 0.017   |
| ≥ 65                     | 267(46.7%)     | 260(47.9%)             | 7(24.1%)               |         |
| Gender                   |                |                        |                        | <0.001  |
| Male                     | 430(75.2%)     | 417(76.8%)             | 13(44.8%)              |         |
| Female                   | 142(24.8%)     | 126(23.2%)             | 16(55.2%)              |         |
| Smoking status           |                |                        |                        | 0.034   |
| Non-smoker               | 305(53.3%)     | 284(52.3%)             | 21(72.4%)              |         |
| Smoker                   | 267(46.7%)     | 259(47.7%)             | 8(27.6%)               |         |
| Histology                |                |                        |                        | 0.002   |
| Adenocarcinoma           | 429(75%)       | 400(74.0%)             | 29(100%)               |         |
| Non-Adenocarcinoma       | 143(25%)       | 117(21.3%)             | 0                      |         |
Table 2 Baseline characteristics of patients treated with pemetrexed-containing chemotherapy

| Clinical characteristics | HER2 | EGFR | ALK/ROS1 | KRAS | P value |
|-------------------------|------|------|----------|------|---------|
| Age, years (median, range) | 55(44–77) | 58(27–80) | 54(37–77) | 64.5(33–80) | 0.002 |
| < 65 | 21(84.0%) | 55(74.3%) | 28(71.8%) | 20(50.0%) |
| ≥ 65 | 4(16.0%) | 19(25.7%) | 11(28.2%) | 20(50.0%) |
| Gender | | | | | |
| Male | 12(48.0%) | 37(50.0%) | 20(51.3%) | 33(82.5%) | 0.004 |
| Female | 13(52.0%) | 37(50.0%) | 19(48.7%) | 7(17.5%) |
| Smoking status | | | | | |
| Non-smoker | 18(72.0%) | 56(75.7%) | 29(74.4%) | 15(37.5%) | <0.001 |
| Smoker | 7(28.0%) | 18(24.3%) | 10(25.6%) | 25(62.5%) |
| PS | | | | | |
| 0–1 | 22(88.0%) | 68(91.9%) | 36(92.3%) | 32(80.0%) | 0.269 |
| ≥ 2 | 3(12.0%) | 6(8.1%) | 3(7.7%) | 8(20.0%) | 0.175 |
| Therapy | | | | | |
| Monotherapy | 4(16.0%) | 9(12.2%) | 3(7.7%) | 9(22.5%) | 0.570 |
| Plus carboplatin | 14(56.0%) | 42(56.8%) | 24(61.5%) | 23(57.5%) |
| Plus cisplatin | 7(28.0%) | 23(31.1%) | 12(30.8%) | 8(20.0%) |
| Maintenance therapy | 7(28.0%) | 18(24.3%) | 13(33.3%) | 5(12.5%) |
| No maintenance | 18(72.0%) | 56(75.7%) | 26(66.7%) | 35(87.5%) |

Table 3 The objective response rate (ORR) and the disease control rate (DCR) of patients treated with pemetrexed-based therapy in four groups

| | HER2 | EGFR | ALK/ROS1 | KRAS | P value |
|---|------|------|----------|------|---------|
| n | 25 | 74 | 39 | 40 | |
| ORR% | 36.0 | 33.8 | 41.3 | 35.0 | 0.896 |
| DCR% | 92.0 | 78.4 | 87.2 | 72.5 | 0.139 |

Discussion

As far as we know, this study is the first study to compare the efficacy of pemetrexed-based chemotherapy between HER2-mutant and groups of EGFR-mutant, ALK/ROS1-rearranged and KRAS-mutant lung adenocarcinoma. We found that patients with HER2-mutant lung cancers had a PFS of 5.1 months that was similar with KRAS-mutant (5.0 months, p = 0.971) lung cancers, and numerically shorter than EGFR-mutant (6.5 months, p = 0.247) and significantly shorter than ALK/ROS1-rearranged (9.2 months, p = 0.004) lung cancers, showing that HER2-mutant lung cancer patients may have poor outcomes with chemotherapy, which strengthen the importance of developing HER2-targeted drugs in this population. We also investigate the clinicopathologic features in patients with advanced HER2-mutant lung adenocarcinomas and found that HER2 mutations were more common in younger patients, females, non-smokers and adenocarcinomas.

Different from HER2 over-expression and amplification, HER2 mutations was found to be a distinct entity in patients with NSCLC [20]. HER2 mutations are found in about 1%–2% of NSCLC [20–22]. In this study, the incidence of HER2 mutations was 5.1% in EGFR/KRAS/ALK/ROS1 negative patients, indicating that HER2 mutations will be enriched in the population without other driver gene mutations. Consistent with our study, a study from the Memorial Sloan Kettering Cancer Center (MSKCC) group [23] showed that in a selected population with EGFR/KRAS/ALK negative, the incidence of HER2 mutations can reach up to 6%. In the early stage resection samples, our previous study [6] showed that the presence of HER2 mutations was not correlated with gender, age, or smoking status. However, another retrospective study [24] of resection samples obtained at Fudan University Shanghai Cancer Center found that the incidence of HER2 mutations can reach up to 5.94% in non-smoking patients with lung adenocarcinoma. Similarly, in biopsied samples from advanced
NSCLC, our study showed that HER2 mutations were more common in non-smokers and lung adenocarcinomas. But HER2 mutations were also frequently detected in younger patients and females in our study. Furthermore, exon20 A775_G776insYVMA was the most frequently alteration.

In the era of targeted therapy, several oncogenic driver mutations were found not only could predict the efficacy of targeted therapy, but also associated with superior outcome of first line pemetrexed chemotherapy, such as ALK and ROS1. Therefore, we further investigate the association of HER2 mutations with the efficacy of pemetrexed-based chemotherapy in patients with HER2-mutant lung adenocarcinomas and found a promising results with YVMA insertion were associated with an inferior PFS (4.2 vs 7.2 months, \( p = 0.085 \)).

Currently, NCCN guideline recommend trastuzumab and afatinib as the targeted therapeutic options for patients with advanced HER2-mutant NSCLC. While, in EUHER2 study [25], afatinib showed a modest response of 18.2% and median PFS of 3.9 months even though this drug has showed response in all 3 assessable patients with HER2-mutant adenocarcinoma in a preliminary study [28]. Meanwhile, several other studies [5, 7, 8] investigated the efficacy of other irreversible pan-HER receptor family inhibitors, dacomitinib, neratinib, or neratinib combining with mTOR inhibitors in advanced NSCLC patients harboring HER2 mutations and showed a moderate response of 12%–21%. Although these ORR or PFS are much diminished compared with those of TKIs directed at other targets in NSCLC, HER2-targeted drugs is still promising. A phase II study recently investigated a novel EGFR/HER2 inhibitor, pyrotinib, in heavily pre-treated patients with HER2-mutant adenocarcinomas and found a promising results with RR of 54.5%(6/11) and median PFS of 6.2 months [9]. Large number cohort study is still needed to validate the efficacy of pyrotinib in this setting.

Our study does have several limitations. First, it was a retrospective study with limited patients number (\( n = 25 \)), while this study presented the real world nature in Chinese population. Second, HER2 mutation testing was performed using the method of ARMS, thus some rare mutations might be missed in our population. Next generation sequencing (NGS), which allows for simultaneous testing for multiple mutations using one platform and one sample, is emerging as an important method for identification of gene mutations in NSCLC, but single-gene sequencing is still more widely used. Thirdly, a substantial part of the patients with HER2 mutations also participate into the...
previous clinical trial of HER2-targeted drugs [9], thus the overall survival might be heavily influenced by the subsequent therapy.

Conclusions
In conclusion, HER2 mutations were more frequent happened in younger patients, females, non-smokers and adenocarcinomas of advanced NSCLC. Patients with HER2-mutant lung adenocarcinomas, especially YVMA insertion, showed poor response to pemetrexed-based chemotherapy. Thus, developing HER2-targeted drugs to improve their poor prognosis is urgently needed for this population.

Additional file

Additional file 1: Study flow chart. (PDF 160 kb)

Abbreviations
ARMS: Amplification refractory mutation system; HER2: Human epidermal growth factor receptor2; NCCN: The National Comprehensive Cancer Network; NSCLC: Non-small cell lung cancers; ORR: The objective response rate; PFS: Progression free survival; RT-PCR: Reverse transcriptase polymerase chain reaction

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Availability of data and materials
All data generated or analyzed during this study are included in this published article and its supplementary information files.

Authors’ contributions
YW and SZ contributed equally in preparing and conducting this research. SR and CZ designed and coordinated the research in this population.

Consent for publication
Not applicable.

Competing interests
No potential conflicts of interest were disclosed.

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