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Outcomes of chemotherapies and HER2 directed therapies in advanced *HER2*-mutant lung cancers

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Abstract

Human epidermal growth factor receptor 2 (HER2, ERBB2) mutations occur in 3% of lung adenocarcinomas. While case reports and series have shown activity of HER2 targeted agents in these patients, little is known about outcomes of chemotherapies. Patients with stage IV *HER2*-mutant lung cancers at Memorial Sloan Kettering were reviewed. Patient demographics, types of *HER2* mutations, duration of systemic treatments and survival were analyzed. We identified 38 patients with *HER2*-mutant lung cancers: median age 62; majority were women (n=24), never smokers (n=22), and all had adenocarcinomas. A 12 base pair in-frame insertion YVMA in exon 20 (p.A775_G776insYVMA) was present in 24 (63%, 95% CI 46–78%) patients. In addition, there were four 9 base pair insertions, one 6 base pair insertion, and five 3 base pair insertions in exon 20, and four single bp substitutions (exon 20 L755F, V777L, D769H, exon 8 S310F). The median overall survival from date of diagnosis of stage IV disease was 2.3 years (95% CI 1.2–2.6). The median duration of chemotherapy was 4.3 months (68 treatments, range 0–21 months): 6.2 months for pemetrexed ± platinum/bevacizumab, 4 months for taxane ± platinum/bevacizumab, 2.6 months for gemcitabine, 3.5 months for vinorelbine. The median duration of HER2 tyrosine kinase inhibitors was 2.2 months (28 treatments, range 0.3–16.3 months). As we search for better targeted therapies for patients with *HER2*-mutant lung cancers, chemotherapy remains an important component of care.

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Keywords

Human epidermal growth factor receptor 2 (HER2); mutation; lung cancer; chemotherapy; targeted therapy

1. Introduction

Mutations in the *human epidermal growth factor receptor 2* (*HER2*, *ERBB2*) occur in 2–3% of lung cancers and have been identified as oncogenic drivers [1–4]. *HER2* mutations most commonly consist of a 12 base pair in-frame insertion YVMA (p.A775_G776insYVMA) in exon 20, leading to downstream activation of the PI3K-AKT and MEK-ERK pathways [2, 3]. This mutation is most commonly found in female patients, never smokers, and those with lung adenocarcinomas [3, 5, 6]. Patients with *HER2*-mutant lung cancers were reported to have a median overall survival of 1.6–1.9 years from the time of stage IV diagnosis [4, 5]. Several reports and case series have demonstrated clinical activity of *HER2*-targeted agents in patients with *HER2*-mutant lung cancers [5, 7–9]. Little is known about outcomes of chemotherapies in patients with *HER2*-mutant lung cancers.

2. Materials and methods

We performed a retrospective study of all patients with *HER2*-mutant lung cancers seen at Memorial Sloan Kettering Cancer Center (MSK) from January 2009 to September 2014. *HER2* mutations were identified via one of the following methods: 1) multiplexed sizing assays for insertions and deletions in *EGFR* and *ERBB2*, 2) mutational hotspot testing by a mass spectrometry-based nucleic acid assay on the Sequenom™ platform for 91 mutations in 8 genes (*EGFR*, *HER2*, *KRAS*, *NRAS*, *BRAF*, *MAP2K1*, *PIK3CA* and *AKT1*), or 3) broad hybrid capture next-generation sequencing via MSK-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) for potentially actionable genetic alterations across 341 cancer-related genes.

For patients with *HER2*-mutant lung cancers who developed metastatic disease, we analyzed clinical and molecular characteristics and their outcomes with conventional chemotherapy and/or *HER2* targeted therapies. We calculated overall survival from the date of diagnosis of stage IV or recurrent metastatic disease using Kaplan-Meier methods. The duration of treatment was defined from the day the first dose of a treatment regimen was given until the day the patient received a different treatment regimen. The duration of treatment for the last treatment regimen ended with the last dose of treatment. We assessed whether the duration of treatment differed across various initial regimens using the Kruskal-Wallis test.

The current study includes five patients from our previously published series of *HER2*-mutant lung cancers [3] as this paper did not examine response to chemotherapy. Eight patients were a part of the Lung Cancer Mutation Consortium [4], five of whom also received dacomitinib as part of a clinical trial [10].

3. Results

3.1. Clinical and molecular characteristics

We identified 64 patients with *HER2*-mutant lung cancers; 38 (59%) developed metastatic disease. An in-frame insertion in exon 20 was identified in 34 patients: 24 with identical 12 base pair insertion YVMA (NM_004448.3: c. 2325_2326ins12, p.A775_G776insYVMA), 4 with 9 base pair insertions, 1 with a 6 base pair insertion, and 5 with 3 base pair insertions. A single base pair substitution was identified in 4 patients and included L755F, V777L, D769H in exon 20 and S310F in exon 8.

Patients were diagnosed with *HER2*-mutant lung cancer at a median age of 62 years (range 37–84). A greater proportion of patients were female (n=24, 63%), racially white (n=27, 71%), and never smokers (n=22, 58%), and all tumors were adenocarcinomas.

3.2. Outcomes with chemotherapies

The median overall survival for patients with metastatic *HER2*-mutant lung cancers was 2.3 years (95%CI 1–2.6) with 21 deaths and a median follow-up of 1.4 years for survivors. The median overall survival for the 24 patients with a 12 base pair insertion YVMA in exon 20 was 1.9 years (95%CI 1.1–3.8). The majority of patients (n=30, 79%) received chemotherapy, including pemetrexed +/- platinum/bevacizumab, taxane +/- platinum/bevacizumab, gemcitabine, vinorelbine, mitomycin, and vinblastine (Fig. 1). Of these, 26 patients received chemotherapy as an initial therapy, and 4 patients received chemotherapy subsequent to a *HER2* targeted therapy.

A total of 119 systemic treatments were given (Table 1). The median duration of chemotherapy given as an initial therapy was 7.5 months (26 treatments) and 3.4 months when given as a subsequent therapy (42 treatments). The most common chemotherapy given was a pemetrexed-containing regimen (26 treatments) followed by a taxane-containing regimen (19 treatments). Pemetrexed-containing regimens also had the longest duration of treatment with the median duration of 6.2 months (18 initial treatments, 8.8 months; 8 subsequent treatments, 3.9 months) followed by taxane-containing regimens (median duration 4 months, 5 initial treatments, 4 months; 14 subsequent treatments, 4 months). The median total time on chemotherapy was 9.8 months (range 0.8–46) among patients who received chemotherapy.

3.3. Outcomes with *HER2* targeted therapies

A total of 23 patients (61%) received one or more *HER2* targeted therapies. *HER2* tyrosine kinase inhibitors (TKI), including dacomitinib, afatinib, neratinib, and lapatinib, were given to 22 patients (58%); 9 received it as an initial therapy, and 13 received it as a subsequent therapy. Of the 28 *HER2* TKI treatments given, those given as an initial therapy (9 treatments) had a median duration of treatment of 5.2 months whereas those given as a subsequent therapy (19 treatments) had a median duration of treatment of 1.8 months. Five patients received trastuzumab over the course of 8 treatments with a median duration of treatment of 2.2 months. All were given as subsequent therapies, and 6 treatments were given concurrently with chemotherapy. Duration of treatment on initial therapies (various

chemotherapy regimens: Pemetrexed, Taxane, Gemcitabine; HER2 TKI and Other regimens) did not differ significantly ($p=0.89$).

4. Discussion

We observed that patients with metastatic *HER2*-mutant lung cancers had a longer median duration of treatment on chemotherapy than a HER2 targeted agent. This trend was consistent for both initial and subsequent lines of therapy. Majority of patients who received a HER2 targeted agent derived either a short duration of benefit or no benefit. However, durable clinical benefit from HER2 targeted agents was clearly seen in some patients, including two on dacomitinib for 13 and 17 months respectively and one on lapatinib for 10 months. One patient received trastuzumab plus vinorelbine for 10 months.

HER2 mutations in the kinase and extracellular domains have been shown to be activating and transforming in lung cancers [11–13]. Case series and phase II clinical trials have reported objective responses to afatinib, dacomitinib, neratinib plus temsirolimus, and trastuzumab in patients with *HER2*-mutant lung cancers [5, 7, 8, 10, 14–17]. However, in a phase II trial of dacomitinib in patients with *HER2*-mutant lung cancers, none of the 13 identical *HER2* insertion YVMA responded [10]. Yet patients with *HER2* insertion YVMA have reported durable responses to single agent afatinib [16]. The molecular complexities seen here suggest that not all *HER2* mutations or HER2 targeted agents are the same, and for reasons yet to be discovered, only a subset of such patients responds to various targeted agents.

This is contrary to multiple randomized trials showing the significant progression-free survival benefits of targeted agents over chemotherapies for patients with *EGFR*-mutant or *ALK*-rearranged lung cancers [18, 19]. Our study suggests the currently available HER2 targeted agents may not have produced the same level of benefit for patients with *HER2*-mutant lung cancers. Chemotherapy remains the standard of care for these patients, and particularly pemetrexed-containing regimens, which are most active against lung adenocarcinomas [20].

The clinical and molecular characteristics observed in this study are consistent with other series. A predominance of female sex, never-smoking history and adenocarcinoma histology are known distinct clinicopathologic characteristics of *HER2*-mutant lung cancers [2, 3, 5]. *HER2* insertion YVMA was found to be the most common subtype accounting for the majority (63%) of *HER2*-mutant lung cancers [3, 10]. Other more rare subtypes of *HER2* mutations were also seen, including an extracellular domain point mutation S310F in exon 8, which was previously shown to be oncogenic in functional analysis [13].

This study has several limitations. Firstly, we did not formally assess radiologic response. Although duration of treatment is a reflection of continual clinical benefit as determined by the clinician, it may be affected by toxicity and treatment interruptions. However, for a retrospective study with heterogeneous imaging modalities and intervals, assessing radiologic response as a surrogate for clinical benefit has its own limitations. Secondly, more patients received first line chemotherapy than targeted agents, and first line therapy is

expected to produce the longest duration of treatment as performance status generally declines with progressing cancer, thus our data may be biased in favor of chemotherapy. However, one could argue that if a HER2 targeted agent truly hits the target, durable clinical benefit should be expected in subsequent lines as well. Furthermore, due to the relatively small sample size, we were not able to adequately compare different types of chemotherapies and HER2 targeted agents. Nevertheless, this study describes a unique population of patients from a single institution with *HER2*-mutant lung cancers, and the data could be used to inform practice and future development of targeted agents.

5. Conclusion

In this age of personalized medicine, chemotherapy remains an integral component of care for patients with metastatic *HER2*-mutant lung cancers. While the few patients we observed to have durable responses to targeted therapy is encouraging and hypothesis generating, further research is warranted to identify more effective targeted agents for specific molecular subsets.

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Abbreviations

TKI	tyrosine kinase inhibitors
HER2	<i>human epidermal growth factor receptor 2</i>

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Highlights

- Outcomes of chemotherapies in patients with *HER2*-mutant lung cancers is unknown
- Patients with stage IV *HER2*-mutant lung cancers at MSK were reviewed
- Median duration of chemotherapy was 4.3 months
- Median duration of HER2 tyrosine kinase inhibitors was 2.2 months
- Chemotherapy remains central to the care of patients with *HER2*-mutant lung cancers

*Chemotherapy: Pemetrexed +/- Platinum/Bevacizumab, Taxane +/- Platinum/Bevacizumab or Abraxane, Gemcitabine +/- Other, Vinorelbine, Mitomycin + Vinblastine

*HER2 TKI: Dacomitinib, Lapatinib, Afatinib, Neratinib +/- Other

*Other: Erlotinib, Immunotherapy +/- chemotherapy, Other

◇ patient is still alive

Figure 1.

The duration of treatments with targeted and non-targeted therapies for patients with metastatic *HER2*-mutant lung cancers.

Table 1

Duration of treatment on each therapy and duration as initial versus subsequent therapy for 38 patients (119 treatments) with metastatic *HER2*-mutant lung cancers.

Regimen and Sequence	Number of treatments	Median Duration (mos)	Range
Chemotherapy*	68	4.3	0–21
Initial	26	7.5	0.8–21
Subsequent	42	3.4	0–20
Pemetrexed +/- Platinum/Bevacizumab	26	6.2	0–21
Initial	18	8.8	1.3–21
Subsequent	8	3.9	0–20
Taxane +/- Platinum/Bevacizumab	19	4	0.7–20.2
Initial	5	4	0.8–20.2
Subsequent	14	4	0.7–16.8
Gemcitabine +/- Other	17	2.6	0–12
Initial	3	4.4	2.5–11.5
Subsequent	14	2.3	0–12
Vinorelbine	2	3.5	2.3–4.6
Initial	0	-	-
Subsequent	2	3.5	2.3–4.6
HER2 TKI	28	2.2	0.3–16.3
Initial	9	5.2	1.3–16.3
Subsequent	19	1.8	0.3–10
Trastuzumab +/- Other	8	2.2	1.3–9.5
Initial	0	-	-
Subsequent	8	2.2	1.3–9.5
Other	15	2.3	0.9–10.6
Initial	3	6.6	5.6–10.6
Subsequent	12	2.1	0.9–7.7

* 4 patients received mitomycin as a subsequent therapy, median 3.2 months (0.7–7.9)