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EGFR exon 20 insertion NSCLC and response to platinum-based chemotherapy

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Abstract

Introduction: In classical *EGFR*-mutant non-small-cell lung cancer (NSCLC), EGFR tyrosine kinase inhibitor (TKI) therapy yields better outcomes than platinum-based chemotherapy. However, *EGFR* exon 20 insertion (ex20ins) NSCLC is relatively resistant to currently available EGFR TKIs. Though platinum-based chemotherapy is the frontline standard of care for *EGFR* ex20ins NSCLC, its efficacy is not fully described.

Study design: A retrospective, single-center, case series

Methods: Patients were identified through an electronic research database at a single institution and included if they had advanced *EGFR* ex20ins NSCLC, received platinum-based chemotherapy for metastatic disease, and had scans evaluable for response. Each patient's demographics, tumor characteristics, and clinical course were recorded. Treatment response was evaluated using RECIST v1.1 criteria, and the PFS was calculated by the Kaplan-Meier method.

Results: Among 27 patients identified with EGFR ex20ins NSCLC at our institution, 18 (67%) received platinum-based chemotherapy for metastatic disease and had scans evaluable for response. These patients received platinum-based chemotherapy in the first-line (N=17,

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94%) and second-line settings (N=1, 6%). The objective response rate (ORR) to platinum-based chemotherapy was 39% (7 of 18 patients; 95% confidence interval [CI] 16-61). The median PFS with platinum-based chemotherapy was 7.1 months (95% CI, 6.3 – 13.7), and the median overall survival was 3.2 years (95% CI, 1.92 – NR).

Conclusions: The efficacy of platinum-based chemotherapy in *EGFR* ex20ins NSCLC is similar to that expected for TKI sensitive *EGFR*-mutant NSCLC. Novel agents designed to specifically target ex20ins mutant EGFR should additionally improve outcomes.

Microabstract

To better understand the efficacy of chemotherapy in treating *EGFR* exon 20 insertion lung cancer, we conducted a retrospective, single-institution case series (n = 29). We found that chemotherapy leads to an average seven months of progression-free survival for these patients. Our findings provide important context for novel therapies being developed for this rare subtype of lung cancer.

Keywords

Epidermal growth factor receptor exon 20 insertion; tyrosine kinase inhibitor; non-small cell lung cancer; platinum-based chemotherapy

Introduction

In non-small-cell lung cancer (NSCLC), molecular profiling and the development of targeted therapies has led to significant improvements for patients with targetable mutations.[1-4] Activating mutations in the epidermal growth factor receptor (*EGFR*) gene occur in 32% of patients with NSCLC.[5] EGFR is a receptor tyrosine kinase that is heavily involved in cellular pathways promoting cell survival, proliferation, and migration. Increased activity of the EGFR protein drives cancer growth. Conformational changes in the classical *EGFR* L858R point mutation and exon 19 deletions destabilize the dormant form of EGFR molecules and shift the equilibrium towards the active form. In contrast, *EGFR* ex20ins mutations are thought to “lock” EGFR molecules in the active state.[6]

The classical *EGFR* L858R point mutation and exon 19 deletions comprise 85-90% of *EGFR* mutant NSCLC, and are frequently responsive to EGFR tyrosine kinase inhibitors (TKIs), with objective response rates (ORR) of up to 80%.[1, 7, 8] This has led to the development of many successful EGFR targeted therapies in recent years, yielding progression-free survival (PFS) of greater than 10 months for first-generation EGFR TKIs and 19 months for third-generation EGFR TKIs (e.g., osimertinib).[1, 9]

Meanwhile, *EGFR* ex20ins NSCLC, which comprises ~4% of all *EGFR* mutant NSCLC, is associated with resistance to available *EGFR* TKIs and therefore confers poorer outcomes for patients.[6, 10, 11] EGFR proteins with ex20ins mutations have binding pockets that are inaccessible to existing EGFR TKIs.[12] Retrospective studies of *EGFR* ex20ins NSCLC treated with first-generation EGFR TKIs such as gefitinib and erlotinib reported ORR between 8 and 27% and a median PFS of less than 3 months.[6, 13] Third-generation *EGFR* inhibitors have slightly better activity against *EGFR* ex20ins NSCLC.[14, 15] Of note, a few

EGFR ex20ins mutation variants, such as A763_Y764insFQEA insertion, are significantly more responsive to existing EGFR TKIs.[16]

Therefore, patients with *EGFR* ex20ins NSCLC are commonly treated with platinum-based chemotherapy as first-line systemic therapy. In clinical trials of EGFR TKIs versus platinum-based chemotherapy in classical *EGFR* mutant NSCLC, platinum-based chemotherapy yields an ORR of about 30% and median PFS of about 5-6 months.[7, 8, 17] While presently chemotherapy is often given concurrently with immune checkpoint inhibitor immunotherapy in first-line NSCLC, the existing indications exclude *EGFR* mutant NSCLC and limited data suggest that immunotherapy monotherapy is ineffective against previously treated *EGFR* mutant NSCLC.[18] Meanwhile, existing literature on the utility of anti-angiogenic therapy in *EGFR* mutant NSCLC is mixed.[19]

Although platinum-based chemotherapy, with or without anti-angiogenic therapy and/or immunotherapy, is a reasonable standard of care for *EGFR* ex20ins NSCLC, its efficacy in this subset of *EGFR* mutant NSCLC is not fully described in the literature. The purpose of this study is to describe the efficacy of platinum-based chemotherapy in *EGFR* ex20ins NSCLC. This will provide important real-world control in light of ongoing clinical trials of new targeted agents designed to target *EGFR* ex20ins insertion.

Methods

This retrospective study was conducted at the Stanford University Hospital & Clinics and Institutional Review Board approval was obtained from Stanford University. Eligible patients were those who were over 18 years of age at the time of diagnosis of *EGFR* ex20ins NSCLC. Using the STAnford medicine Research data Repository clinical database (STARR), all patients with EGFR ex20ins NSCLC who received platinum-based chemotherapy and had scans evaluable for treatment response were identified from December 1, 2013 to July 31, 2020.

Descriptive data (e.g., demographics, tumor characteristics, treatment courses) were collected for each patient. Of the 27 patients identified with *EGFR* ex20ins NSCLC, 18 received platinum-based chemotherapy and had scans that were evaluable for response. Molecular testing predominantly consisted of tissue testing with next-generation sequencing (NGS) through the Stanford Solid Tumor Actionable Mutation Panel (n = 14, 78%). A smaller subset had tissue PCR-based testing (n = 4, 22%) when diagnostics were performed outside our institution. Tumor measurements were made by clinical investigators MPS and JVA and subsequently reviewed by medical oncology investigator JWN. Tumor responses were determined using RECIST 1.1 criteria, and PFS was calculated using the Kaplan-Meier method. Statistical significance was defined at a $p < 0.05$.

Results

Patient demographics, characteristics, and treatments for the cohort of 18 patients are shown in table 1. The average age was 60 years, two-thirds were women, and less than a quarter had any smoking history. The histotype was adenocarcinoma in all cases, and all presented with stage IV disease at the time of systemic therapy. Fourteen (78%) patients underwent

targeted NGS testing and the most commonly identified subtypes of *EGFR* ex20ins mutation included V769_D770insASV (28%) and A767_V769dup (28%). The remaining 4 insertion points were not characterized as these patients underwent PCR-based testing. Over half the patients had bone metastases, and fewer than half had metastases to liver, brain, or adrenal glands.

Most patients (17 of 18) received platinum-based chemotherapy as the first-line of therapy, whereas one patient received it as second-line therapy after progression on afatinib, which was given at an outside institution. Most patients (17 of 18) received carboplatin with pemetrexed, and one patient received carboplatin with paclitaxel. A third of the patients (6 of 18) had bevacizumab added to their chemotherapy regimen, and two patients had pembrolizumab added to their chemotherapy regimen.

The objective response rate to platinum-based chemotherapy was 44% (8 partial response, 10 stable disease) with an average 22% reduction (s.d.15.6) in tumor burden, as shown in figure 1. The median PFS with platinum-based chemotherapy was 7.1 months (95% CI, 6.3 – 13.7), as shown in Figure 2. At the time of our analysis (data cutoff: July 31, 2020), 9 patients had died, and the median overall survival was 3.2 years (95% CI, 1.92 – NR). A sensitivity analysis excluding the two patients who received carboplatin/pemetrexed/pembrolizumab showed consistent results (data not shown).

In the six patients who received bevacizumab with platinum-based chemotherapy, the mean tumor burden reduction was 30%, the ORR was 50%, and the median PFS was 6.2 months. In the two patients who received pembrolizumab with platinum-based chemotherapy, best response was stable disease, and the PFS were 2.3 months and 14.5 months.

In the five patients harboring the V769_D770insASV mutation, the mean tumor burden reduction was 21%, the ORR was 20%, and the median PFS was 5.2 months. In the five patients harboring the A767_V769dup mutation, the mean tumor burden reduction was 21%, the ORR was 40%, and the median PFS was 7.8 months.

Discussion

In this single-institution retrospective study, we describe the efficacy of platinum-based chemotherapy in 18 patients with *EGFR* ex20ins NSCLC. The ORR was 44%, median PFS was 7.1 months, and median OS was 3.2 years. These efficacy results are similar to those with platinum-based chemotherapy in EGFR TKI sensitive *EGFR* mutant NSCLC (i.e., L858R, ex19del).[7, 8, 17] In the subgroup of 6 patients who received bevacizumab in combination with platinum-doublet therapy, the ORR and median PFS were not numerically different from the analysis of the overall population. In the two patients who received platinum-doublet chemotherapy in combination with pembrolizumab, both had stable disease, though notably one patient with high PD-L1 expression had a prolonged PFS of 14.5 months. In the subgroup of five patients harboring the A767_V769dup mutation, the ORR and median PFS were only slightly numerically greater than those in the subgroup of five patients harboring the V769_D770insASV mutation. Given the small sample size,

we were unable to explore the association of clinical outcomes with therapy regimens, metastatic sites, specific ex20ins mutation, or presence of comutations (e.g. *TP53*).

Two recently published retrospective studies have described the clinical course of *EGFR* ex20ins NSCLC in Hispanic and Chinese patients. In the first study, 79 Hispanic patients with *EGFR* ex20ins NSCLC were treated with first-line EGFR TKI therapy or platinum-based chemotherapy with or without bevacizumab. Of the 50 patients who received first line platinum-based chemotherapy, the PFS was 6.9 months, consistent with the findings in our study. Unlike our study, 36% of tumors in this study had co-existing classical sensitizing *EGFR* mutations, which is much higher than previously described.[20] In another study, 104 Chinese patients with *EGFR* ex20ins NSCLC who received first-line platinum-based chemotherapy demonstrated an ORR of 19.2% and a median PFS of 6.4 months, with the ORR being lower but the PFS being similar to our study.[21]

Limited data describe efficacy of single-agent immunotherapy in *EGFR* ex20ins NSCLC. A series of 36 patients with *EGFR* ex20ins NSCLC demonstrated an ORR of 25% and median PFS of 2.9 months. These values were numerically better than what was observed in 38 patients with classical EGFR sensitizing mutations, where the observed ORR was 0% and the median PFS was 1.9 months.[22] In our study, only two patients received immunotherapy in combination with platinum-doublet chemotherapy and the value of this strategy in patients with *EGFR* ex20ins NSCLC needs further study.

Though existing EGFR TKIs have failed to improve the outcomes for patients with *EGFR* ex20ins NSCLC, novel TKIs designed to target the ex20ins EGFR protein are being tested against platinum-based chemotherapy in the frontline setting. These first line clinical trials will provide prospective data on the efficacy of platinum-based chemotherapy in *EGFR* ex20ins NSCLC. For these novel agents to be proven superior to first-line platinum chemotherapy, response rates over 40% and/or PFS over 8 months will likely be needed. Mobocertinib (TAK-788) is a promising novel TKI that covalently binds to EGFR molecules with selectivity towards ex20ins mutant *EGFR* over wild-type *EGFR*. Preliminary results from a phase II open-label, cohort expansion showed that mobocertinib demonstrated a high disease control rate of 86% (NCT02716116). Mobocertinib is now being studied through the global EXCLAIM extension study in 91 previously treated patients with advanced *EGFR* ex20ins NSCLC and is also being tested head-to-head against first-line carboplatin and pemetrexed in the EXCLAIM-2 study (NCT04129502).

Amivantamab, a novel bispecific antibody targeting EGFR and mesenchymal epithelial transition factor (MET) receptor, was recently approved for patients with locally advanced or metastatic *EGFR* ex20ins NSCLC after progression on or after platinum-based chemotherapy. This accelerated approval was based on results from the multicenter, multicohort, non-randomized, open label clinical trial CHRYSALIS. In the subset of 81 patients who had progressed on platinum-based chemotherapy, the ORR was 40% and the median duration of response was 11.1 months (NCT02609776). Based on these results, amivantamab in the second-line setting for *EGFR* ex20ins NSCLC yields an ORR similar to what we observe with platinum-based chemotherapy in the first-line setting. These results suggest that amivantamab may be efficacious against *EGFR* ex20ins as first-line therapy. A

phase III study of combination amivantamab and carboplatin-pemetrexed therapy compared with carboplatin-pemetrexed in advanced *EGFR* ex20ins NSCLC is currently underway (NCT04538664).

Limitations of our study include a small cohort, retrospective approach, and conduct within a single institution. Due to not all tumors undergoing NGS testing, mutation subtypes were available for most but not all patients limiting possible comparison of platinum-based chemotherapy efficacy between groups.

Regarding our institutional practice patterns for *EGFR* Ex20ins NSCLC, our preferred platinum regimen includes carboplatin and pemetrexed, with or without bevacizumab. If immunotherapy is desired, then the four drug "IMpower 150" regimen consisting of atezolizumab, bevacizumab, carboplatin and paclitaxel could be considered; however, our institutional preference is generally to avoid PD-(L)1 inhibitors in patients with EGFR mutations due to uncertain effectiveness, except perhaps in patients with a smoking history or high PD-L1 expression.

Conclusion

EGFR ex20ins NSCLC has proven resistant to currently available EGFR TKIs, yielding significantly worse outcomes for patients when compared to those of classical *EGFR* mutant NSCLC. Our study adds real-world data to the literature of platinum-doublet efficacy in patients with *EGFR* ex20ins NSCLC. Until randomized studies of novel TKIs are complete, the current first-line standard of care for *EGFR* ex20ins NSCLC remains a platinum-based chemotherapy backbone, which has similar efficacy in this subtype as in other *EGFR* mutant NSCLC. Novel drugs to target *EGFR* ex20ins NSCLC will hopefully soon be approved and improve the outcomes for patients.

Clinical practice points

EGFR TKI therapies lead to better outcomes than platinum-based chemotherapy for patients with classical *EGFR* mutant NSCLC. However, in *EGFR* ex20ins NSCLC, currently available TKI therapies have proven ineffective, and chemotherapy is used instead. The efficacy of platinum-based chemotherapy in ex20ins NSCLC has not been fully described in the literature. In our study, we found that the objective response rate (ORR) to platinum based-chemotherapy was 39%, and the median progression-free survival was 7.1 months, suggesting that the efficacy of platinum-based chemotherapy in *EGFR* ex20ins NSCLC is similar to that expected for TKI sensitive EGFR-mutant NSCLC. Our study adds real-world data to the literature of platinum-doublet efficacy in patients with *EGFR* ex20ins NSCLC. Until randomized studies of novel TKIs are complete, the current first-line standard of care for EGFR ex20ins NSCLC remains a platinum-based chemotherapy backbone. Our preferred platinum regimen includes carboplatin and pemetrexed, with or without bevacizumab. We anticipate that novel therapies designed to specifically target ex20ins mutant EGFR will further improve outcomes.

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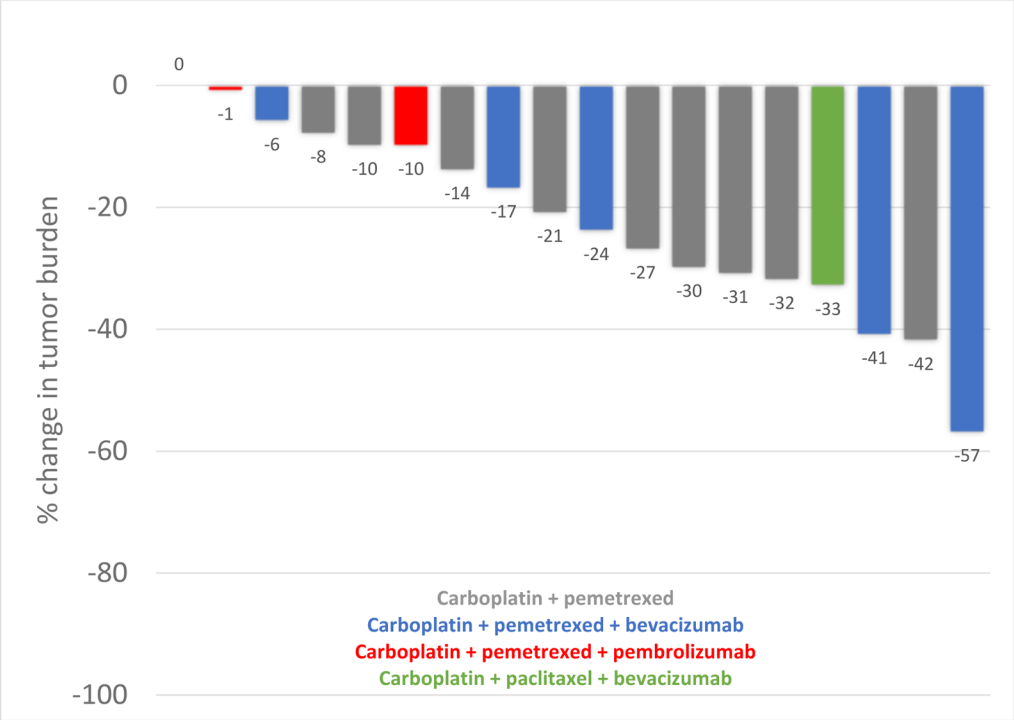

Figure 1.

Best change in tumor burden for 18 patients with *EGFR* ex20ins NSCLC treated with platinum-based chemotherapy

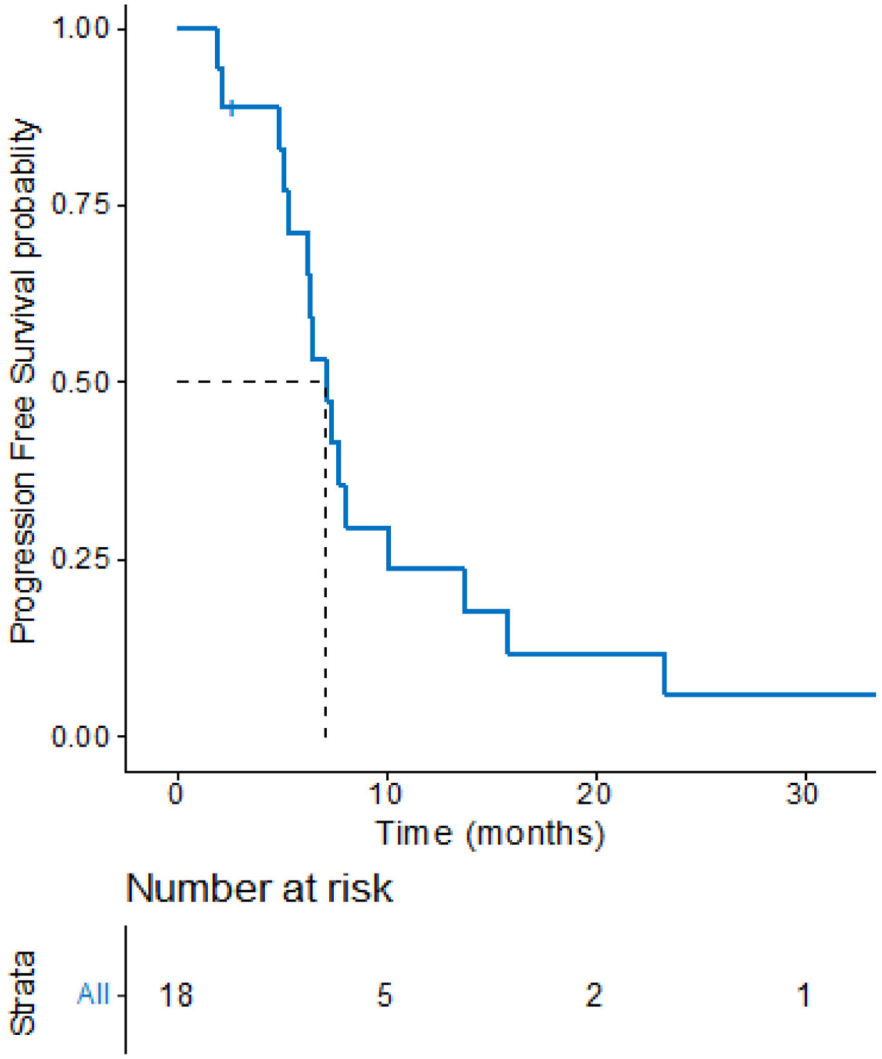

Figure 2.
PFS Kaplan-Meier curve of 18 patients with *EGFR* ex20ins NSCLC treated with platinum-based chemotherapy

Table 1.

Patient Characteristics and Treatments

Characteristic	n (%)
Total	18
Male/Female	6 (33) / 12 (67)
Race/ethnicity	
Non-Hispanic white	7 (39)
Hispanic	4 (22)
Asian	7 (39)
Mean age at diagnosis	60y (range 32-81)
Positive smoking history	4 (22)
Histological subtype	
Adenocarcinoma	18 (100)
Ex20ins mutation subtype	
V769_D770insASV	5 (28)
A767_V769dup	5 (28)
S768_D770dup	2 (11)
p.N771delinsGF	1 (6)
M766_A767ins	1 (6)
Unknown	4 (22)
Co-mutations and other tumor markers	
TP53	7 (39)
PIK3CA	1 (6)
APC	1 (6)
ERBB2	1 (6)
PD-L1 (high expression, > 50%)	1 (6)
CDK4 amplification	1 (6)
Stage at systemic treatment initiation	
IV	18 (100)
Location of metastases	
Brain	3 (17)
Bone	11 (61)
Liver	5 (28)
Adrenals	2 (11)
Prior local therapy	
Surgery	1 (6)
Radiation	14 (78)
Platinum-based chemotherapy regimen	
Carboplatin + pemetrexed	10 (56)
Carboplatin + pemetrexed + bevacizumab	5 (28)

Characteristic	n (%)
Carboplatin + pemetrexed + pembrolizumab	2 (11)
Carboplatin + paclitaxel + bevacizumab	1 (6)
Line of therapy	
First-line	17 (94)
Second-line	1 (6)