Clinical Oncology: Case Reports

Case Report

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Cetuximab in Patients with Non-Small Cell Lung Cancer and EGFR Exon 20 Insertion Alterations

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Abstract

Epidermal Growth Factor Receptor (EGFR) exon 20 insertion alterations represent 4%-10% of all EGFR mutations in Non-Small Cell Lung Cancer (NSCLC) and result in resistance to standard EGFR-directed therapies. EGFR exon 20 insertions restrict the size of the kinase pocket, prohibiting the entry of approved EGFR kinase inhibitor drugs. Structural In Silico modeling also predicts that EGFR exon 20 insertion anomalies increase attractive electrostatic dimerization, hence stabilizing the activating dimer configuration. EGFR antibodies such as cetuximab that interfere with dimerization may lead to responses. We identified three non-smoking patients with NSCLC and EGFR exon 20 insertions treated with cetuximab-based therapy. All three patients demonstrated clinical benefit. A 58-year-old woman achieved prolonged stable disease lasting 9 months, while a 76-year-old woman and 38-year-old man maintained a partial response with progression-free survivals of 13 months and 32 months, respectively. In conclusion, cetuximab merits further investigation as it appears to be an additional promising therapy for overcoming EGFR exon 20 insertion-related resistance.

Keywords

Cetuximab; EGFR; Exon 20 insertion; NSCLC

Introduction

Erlotinib is an effective small molecule EGFR inhibitor that is approved for NSCLC harboring an exon 19 deletion or exon 21 (L858R) substitution mutation [1,2]. However, resistance can develop through additional mutations, such as the EGFR T790M, which can be overcome by osimertinib, now often used as front-line treatment in EGFR-mutated NSCLC [3]. EGFR exon 20 insertions represent 4%-10% of all EGFR alterations in NSCLC, and mediate resistance to several approved EGFR inhibitors, with response rates of only 3%-9% for erlotinib, gefitinib, and the second-generation EGFR inhibitor afatinib [4-6]. Recently, however, two drugs have been approved for this indication, including a bispecific EGFR/MET antibody amivantamab, and a small molecule inhibitor mobocertinib, based on response rate of ~40% and 28%, respectively.

In silico modeling demonstrated that the EGFR exon 20 insertions result in an activated kinase with a small pocket into which most kinase inhibitors do not fit, therefore necessitating a kinase inhibitor of smaller size, such as poziotinib [4-8]. Computer simulations also show that the EGFR exon 20 insertion stabilizes the active dimer configuration, hence possibly sensitizing to an agent such as an EGFR antibody that prevents dimerization [7]. Anecdotal cases further suggest that the EGFR antibody cetuximab may be able to overcome exon 20 insertion resistance in the clinic [5,7,9].

We present a case series of three patients with EGFR exon 20 insertions who showed benefit from cetuximab-based treatment.

Methods

Molecular tumor board

Patients with EGFR exon 20 insertion alterations were identified from the PREDICT and the molecular tumor board database (NCT02478931). We followed Institutional Review Board guidelines for data analysis and any investigational studies for which patients provided written informed consent.

Genotyping results and interpretation of the molecular results

In each of the three cases, an EGFR exon 20 insertion was identified via next generation sequencing (NGS) of tumor tissue: EGFR exon 20 insertion (H773_V774lnsPH) (case 1); EGFR exon 20 insertion (H773_V774insPH) (Case 2); EGFR exon 20 (D770_P772delsinKG) (Case 3). These EGFR exon 20 insertions represent <10% of EGFR alterations in lung cancer [5].

Results

Case 1

A76-year-old non-smoking woman (history of chronic lymphocytic leukemia) was noted to have increasing lung ground-glass opacities by Computerized Tomographic (CT) scan. Transbronchial biopsy showed adenocarcinoma. Next Generation Sequencing (NGS) of lung cancer tissue (Foundation Medicine, 324 genes, https://www.foundationmedicine.com/genomic-testing) showed EGFR exon 20 insertion (H773_V774lnsPH) without other alterations; NGS of blood-derived circulating tumor DNA (ctDNA) (Guardant Health, https://guardanthealth.com/, 73 genes), NRAS G13V, NF1 R69fs, NF1 S340fs, and BRCA2 E1335fs mutations. The patient declined therapy for eight months, when repeat CT scan showed a growing left lung mass; repeat biopsy demonstrated adenocarcinoma. The patient was started on cetuximab for EGFR exon 20 insertion and trametinib for NRAS and NF1 mutations. She was on therapy for 13 months with a partial response (Figure 1). The patient died due to septic shock from colon perforation, which was felt to be unrelated to therapy or her cancer. Side effects were limited to rash.

Case 2

A 58-year-old non-smoking woman was diagnosed with metastatic NSCLC after presenting with cough. Pleural nodule biopsy showed an EGFR exon 19 deletion (L747_P753>S). She was treated with erlotinib (>2 years) followed by osimertinib (16 months) until

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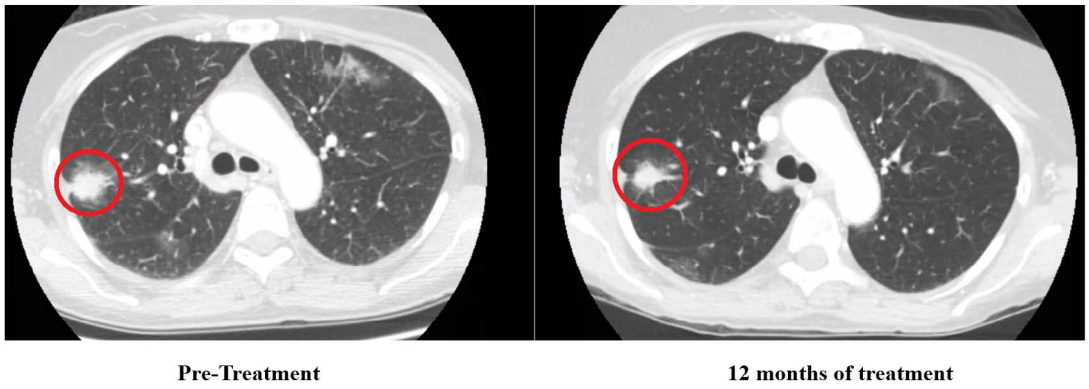

Figure 1: CT scans of the lungs demonstrate a partial response to cetuximab-based therapy in a 76 year-old woman with an EGFR exon 20 insertion (H773_V774InsPH) on tissue NGS of her NSCLC. Progression-free survival was 13 months; Left: Prior to initiation of therapy; Right: Following 12 months of therapy.

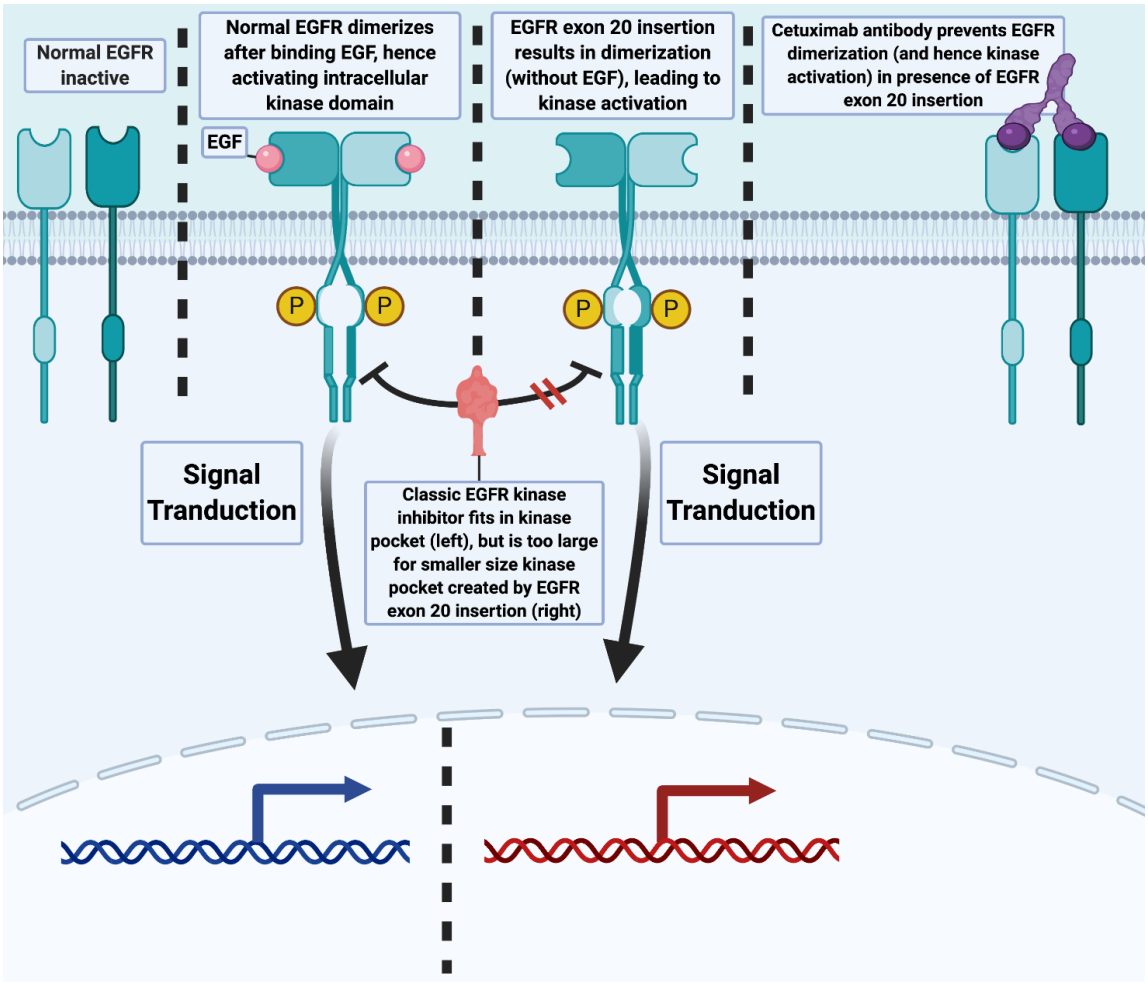

Figure 2: Functional impact of EGFR exon 20 insertion alterations. Normal EGFR is activated after EGF ligand binds to its receptor. Binding of EGF to EGFR as well as EGFR alterations cause the EGFR kinase to be activated (with the latter not requiring EGF ligand binding); EGFR small molecule inhibitors fit in the kinase pocket and suppress activation of the kinase enzyme. However, when an EGFR exon 20 insertion occurs, the activated EGFR kinase pocket that forms is too small to allow entry of classic, approved EGFR small molecule kinase inhibitors, hence resulting in resistance. EGFR exon 20 insertions also bring the EGFR dimerization domains together, thereby activating the kinase region; the EGFR antibody cetuximab interferes with EGFR dimerization, short circuiting EGFR activation.

progression. Repeat biopsy showed a new EGFR exon 20 insertion (H773_V774insPH) (Foundation Medicine, 324 genes NGS) (https://www.foundationmedicine.com/genomic-testing) along with TP53 G244A and SPTA1 alterations. The patient was started on afatinib and cetuximab, with stable disease lasting nine months. Side effects included only low-grade diarrhea and abdominal pain.

Case 3

A 38-year-old non-smoking man presented with back pain due to cord compression and bone lesions. Left iliac biopsy showed metastatic lung adenocarcinoma harboring an EGFR exon 20 alteration (D770_P772delsinKG) {Caris Life Sciences (https://www.carislifesciences.com/cmi-overview/)}. He received thoracic spine and sacrum radiation. He was started on carboplatin, paclitaxel, bevacizumab, and cetuximab. Following three months of therapy, the chemotherapy was discontinued and he was transitioned to maintenance cetuximab and bevacizumab, which he received for a total of 29 months with a partial response. Side effects were limited to skin toxicity, which necessitated a two-month drug holiday (after eight months of cetuximab and bevacizumab); he resumed these therapeutic antibodies without further significant adverse events. Treatment was discontinued after a total of 32 months from its start, due to progression. There were no other serious side effects.

Patient updates

As noted in the patient histories, all three patients had non-smoking NSCLC and all benefitted from cetuximab-based therapy. The first patient (age 76) achieved a PR lasting 13 months (Figure 1) and then died of unrelated causes. The second patient (age 58) had stable disease that lasted 9 months. The third patient (38-year-old) attained a PR that lasted 32 months. The most common side effect was rash.

Discussion

EGFR exon 20 insertions are resistant to classic EGFR small molecule inhibitors and are associated with poor NSCLC outcomes. Structurally, this alteration results in a small kinase domain that is not accessible to conventional kinase inhibitors [4-8]. Combination therapy with erlotinib and cetuximab has previously been studied in a clinical trial as a means to improve EGFR targeting, and a partial response ongoing at 42 months was reported in a NSCLC with an EGFR exon 20 insertion alteration [7]. A separate study of EGFR exon 20 insertion NSCLC treated with afatinib with cetuximab noted objective responses in three of four patients, though afatinib alone is ineffective [5,9]. These observations are consistent with *In Silico* modeling observations showing that the EGFR exon 20 insertion activates EGFR by bringing the dimerization domains together, while EGFR antibody attenuates dimerization (Figure 2) [7]. In our case series, the three cetuximab-treated patients with EGFR exon 20 insertions had a PFS of 9, 13 and 32 months, respectively. The main side effect was rash.

Poziotinib is a small size novel kinase inhibitor designed to overcome EGFR exon 20 insertion resistance by fitting into the small kinase pocket created by EGFR exon 20 insertions [6,8]. In the clinic, it has activity, but reported median PFS is 5.6 months in EGFR exon 20 insertion NSCLC [5,6,8]. Reviews of other molecules show the following 5: luminespib, a heat shock protein 90 inhibitor, 17% response rate (2.9 month median PFS); and TAK-788 (mobocertinib), a novel small molecule inhibitor, 28% response rate (https://www.targetedonc.com/view/fda-approves-mobocertinib-for-egfr-exon-20-positive-mnsclc). Amivantamab is of special interest. It is a bispecific EGFR-MET antibody that has shown promising preclinical and clinical activity in patients with EGFR exon 20 insertions [10] and was recently granted for accelerated approval by the Food and Drug Administration with a 40% response rate (median duration=11 months) (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-amivantamab-vmjw-metastatic-non-small-cell-lung-cancer).

In conclusion, while our sample size is small, it is of interest that all three patients treated had clinical benefit from cetuximab, including two partial responses, and that the benefit duration was between 9 and 32 months. Furthermore, responses, albeit anecdotal, to cetuximab in other patients with NSCLC and EGFR exon 20 insertions have also been reported, including patients with partial responses ongoing at 3.5 years [5,7]. While afatinib itself has a response rate of ~9% in EGFR exon 20 insertion NSCLC, the combination of cetuximab and afatinib resulted in objective responses in 3 of 4 such patients [5,9]. Interestingly, an exceptional response to a trastuzumab-based (ERBB2 antibody) regimen has been documented in a NSCLC with an analogous exon 20 alteration (insertion 774-775 AYVM) in a different Erb receptor family member-ERBB2 [10]. These observations demonstrate the value of molecular tumor board discussions, *In Silico* modeling, and of individualized therapy [7,11-17]. Prospective cetuximab evaluation in EGFR exon 20 insertion NSCLC is warranted.

Disclaimer

Ethics approval and consent to participate

This study was performed in accordance with the UCSD IRB guidelines for data analysis and for any investigational treatments for which patients gave consent.

Consent for publication

Not applicable.

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Disclosures/Competing interests

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Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

MN performed the chart review and wrote the manuscript. RK

conceptualized the study and wrote the manuscript. SK reviewed the manuscript.

Disclosures

Shumei Kato serves as a consultant for Foundation Medicine. Speaker's fee: Roche. Research grant: ACT Genomics, Sysmex, Konica Minolta, OmniSeq. Razelle Kurzrock has research funding from Incyte, Genentech, Merck Serono, Pfizer, Sequenom, Foundation Medicine, Guardant Health, Grifols, and Konica Minolta, as well as consultant fees from LOXO, X-Biotech, Actuate Therapeutics, Genentech and NeoMed. She receives speaker fees from Roche, and has an equity interest in IDbyDNA and Curematch, Inc. Mina Nikanjam received salary support from Genentech and owns Genentech stock.

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