EGFR Exon 19 Deletion in Pancreatic Adenocarcinoma Responds to Erlotinib, Followed by T790M-Mediated Resistance

Michael Cecchini, MD^{a,b}; Jeffrey Sklar, MD, PhD^{b,c}; and Jill Lacy, MD^{a,b}

Abstract

The prognosis of metastatic pancreatic cancer remains poor despite recent advances in treatment with multidrug chemotherapy regimens. Use of immune checkpoint inhibitors and molecular targeted therapies has so far been disappointing. This report describes a patient with chemotherapy-refractory metastatic pancreatic ductal adenocarcinoma (PDAC) whose tumor was characterized by an activating mutation in exon 19 of the epidermal growth factor receptor (*EGFR*). He experienced response to erlotinib for 10 months, and then developed disease progression in association with emergence of the *T790M* mutation. Activating *EGFR* mutations in cancers other than lung are uncommon, but when present may predict response to EGFR tyrosine kinase inhibitors (TKIs). Development of the *T790M* mutation in this case suggests that EGFR-targeted TKIs may follow similar patterns of resistance regardless of tumor type. Although actionable mutations are detected infrequently in PDAC, this case illustrates the potential benefit of offering genomic analysis to all patients with advanced disease.

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Pancreatic ductal adenocarcinoma (PDAC) remains a highly lethal disease. Approximately 92% of patients with PDAC will die with advanced disease within 5 years of diagnosis when accounting for all disease stages.¹ Despite recent incremental advances in the treatment of metastatic PDAC with 5-fluorouracil (5FU), irinotecan, oxaliplatin, and leucovorin (FOLFIRINOX) or gemcitabine plus nab-paclitaxel, median survival remains <1 year.^{2,3} Moreover, second-line treatment options are of limited benefit, and the use of immunotherapies and molecularly targeted drugs has proven disappointing. Widespread use of genomic analysis to identify actionable mutations in PDAC has been constrained due to challenges with tissue acquisition and the low likelihood of identifying an actionable target. Although recent studies indicate that genomic analysis is technically feasible in most patients with PDAC, more information is needed to determine whether these

tumors respond to targeted therapy when actionable mutations are identified.⁴ This report describes a patient with PDAC whose tumor was characterized by an exon 19 deletion and who experienced a sustained response to erlotinib.

Case Summary

A 57-year-old Caucasian man with type II diabetes mellitus presented with increasing insulin requirements, jaundice, and weight loss. Imaging revealed a pancreatic head mass with <180° of superior mesenteric vein abutment and no evidence of distant metastases. A biopsy confirmed PDAC. He received 6 cycles of neoadjuvant FOLFIRINOX followed by pancreaticoduodenectomy with negative margins and 6 cycles of adjuvant FOLFIRINOX. Surgical pathology revealed ypT3N1Mx (stage IIB) adenocarcinoma.

From ^aDepartment of Medicine, Section of Medical Oncology, Yale School of Medicine; ^bYale Cancer Center; and ^cDepartment of Pathology, Yale School of Medicine, New Haven, Connecticut.
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Correspondence: Michael Cecchini, MD, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06510. E-mail: michael.cecchini@yale.edu

Eight months after completion of adjuvant therapy, PET imaging revealed recurrent disease in the postsurgical bed and multiple liver metastases. He began gemcitabine and nab-paclitaxel for metastatic PDAC, but after 54 weeks imaging revealed progression of hepatic metastases. Subsequently, he was treated with second-line FOLFIRINOX. After 38 weeks, imaging again showed progression of hepatic metastases. He received third-line therapy with docetaxel and irinotecan for 2 weeks, but this therapy was complicated by febrile neutropenia.

A tumor specimen from the pancreaticoduodenectomy was sent to Foundation Medicine (Cambridge, MA) for genomic analysis, which revealed an activating mutation in exon 19 (L747_P753>S) of *EGFR* with a mutation allele frequency (MAF) of 16%. Mutations were also detected in *CDKN2A* (splice site 144_153del10) with an MAF of 15%, *TP53* (F113C) with an MAF of 7%, and amplifications of *PRKCI* and *TERC*. After the sequencing results, he began erlotinib at 150 mg daily. He subsequently developed grade 2 acneiform drug eruption, which responded to triamcinolone and doxycycline. CT imaging revealed a partial response (PR) by RECIST at 8 and 24 weeks after starting erlotinib. His CA 19-9 level declined from 29,156 to 387 U/mL at 24 weeks (Figure 1). At 32 weeks, imaging showed a sustained PR, although his CA 19-9 level increased to 778 U/mL. At 40 weeks, his CA 19-9 level had increased to 3,847 U/mL and CT imaging revealed unequivocal disease progression by RECIST, with increasing size and number of hepatic metastases.

After disease progression on erlotinib, a repeat liver biopsy revealed an *EGFR* T790M mutation by TaqMan assay (Applied Biosystems, Foster City,

CA). At the time of T790M confirmation, his CA 19-9 level had increased to 9,822 U/mL. He began treatment with osimertinib at 80 mg daily. After 8 weeks of this treatment, his CA 19-9 level had increased to 52,436 U/mL, and CT imaging revealed unequivocal disease progression with increasing size and number of hepatic metastases, including the T790M biopsy site, which had increased from 2.8 to 4.5 cm. After 8 weeks, osimertinib was discontinued, and he was enrolled in a phase I clinical trial with combined anti-PD-L1 and anti-CD73 antibodies. However, he did not experience a response and is currently receiving best supportive care.

Discussion

This case describes a patient with metastatic PDAC and an activating *EGFR* mutation that had a partial and sustained response to erlotinib monotherapy followed by T790M resistance. This is the first report of *EGFR*-mutated PDAC developing T790M-mediated resistance to a first-generation tyrosine kinase inhibitor (TKI). The course described here supports the conclusions that activating *EGFR* mutations in PDAC respond to *EGFR* TKIs, and resistance to therapy may be due to similar mechanisms to those seen in non-small cell lung cancer (NSCLC).

The genomic landscape of PDAC is dominated by recurring oncogenic lesions in *KRAS*, *p53*, *CDKN2A*, and *SMAD4*.⁵ Among these 4 well-known cancer genes, activating mutations in *KRAS* are nearly ubiquitous and present in >90% of cases.⁵ Numerous other genes are mutated or amplified in PDAC, but most of these occur at low allelic fractions, reflecting marked intratumoral heterogeneity and a complex mutational landscape.⁵ Although *EGFR* has been suggested to play a role in the pathogenesis of PDAC, because it is frequently overexpressed and may be associated with a poor prognosis, the presence of activating mutations in *EGFR* are notably rare.⁶⁻⁹

EGFR overexpression in PDAC provided the rationale for evaluating erlotinib in this disease. In a large randomized phase III trial comparing gemcitabine monotherapy with gemcitabine plus erlotinib, there was a survival benefit of just 10 days with the combination.⁶ Although the benefit with the addition of erlotinib achieved statistical significance ($P=.038$), the clinical impact of erlotinib in

Figure 1. Timeline for the CA 19-9 tumor marker over the past 20 months. The area highlighted in green, starting at month 4, represents the period on erlotinib therapy. The period after the green box represents the time on osimertinib.

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advanced PDAC is widely regarded as negligible.⁶ Given the high frequency of mutated *KRAS*, which predicts resistance to *EGFR*-directed therapies, and the low frequency of activating mutations in *EGFR*, the limited efficacy of erlotinib in this unselected population of patients with PDAC is expected.

Our patient's tumor was characterized by the unusual combination of a wild-type *KRAS* gene with an activating *EGFR* mutation. The mutation in this case is a deletion in exon 19, which encodes the kinase domain of the receptor. Deletions in exon 19 of *EGFR* are well described and represent approximately 40% of activating *EGFR* mutations seen in lung adenocarcinoma, in which they confer sensitivity to TKIs.¹⁰ Based on these genomic results, this patient was treated with erlotinib monotherapy. Remarkably, he had a partial and sustained response to erlotinib lasting for 280 days, which is comparable to *EGFR*-mutant lung cancer, wherein median progression-free survival (PFS) with TKIs is approximately 285 days.¹⁰ The durability of this patient's response to erlotinib after 2 lines of chemotherapy compares favorably with the PFS reported for the recently approved second-line therapy with 5FU/liposomal irinotecan (95 days) and for first-line therapies with FOLFIRINOX, gemcitabine/nab-paclitaxel, and gemcitabine/erlotinib (192, 165, and 115 days, respectively).^{2,3,6,11}

Activating mutations in *EGFR* are most common in NSCLC. When the mutation is present in exon 19 or 21, which represents >96% of *EGFR* mutations, the response rate to *EGFR* TKIs exceeds 70%.¹⁰ Outside of NSCLC, *EGFR* mutations in exons 19 through 21 are rare, but have been described in cancers of the pancreas, head and neck, esophagus, biliary tract, prostate, colon, and ovaries, as well as in sarcomas and papillary renal cell carcinoma.^{12–18} Mutations in *EGFR* are present in rare cases of patients with PDAC, with The Cancer Genome Atlas (TCGA) database reporting *EGFR* mutations in 1 of 149 tumors (0.7%) and the COSMIC database reporting *EGFR* mutations in 6 of 1,599 (0.37%) PDACs.^{7–9,14,19,20} In contrast, Wang et al²¹ reported *EGFR* mutations in 49 of 88 (56%) unselected Taiwanese patients with metastatic PDAC; this result conflicts with the low prevalence reported in the TCGA and COSMIC databases and needs further validation. The presence of actionable mutations in *EGFR* outside of lung cancer has typically been detected by retrospective analysis. A review of the lit-

erature for actionable *EGFR* mutations in non-lung tumor types treated with *EGFR*-directed therapies is outlined in Table 1 (with the exception of Wang et al).^{14,15,17,18,22} Table 1 includes 2 cases of PDAC, which were retrospectively analyzed based on disease stabilization for >100 days on a phase II study of capecitabine plus erlotinib.¹⁴ Notably, in our case, a PR was achieved with erlotinib monotherapy. These reports and our experience both support the use of *EGFR* TKIs for non-lung cancers with actionable *EGFR* mutations.

The mechanism for acquired resistance to *EGFR* TKIs is well established in lung cancer and most commonly involves either development of the T790M mutation or *MET* amplification.^{23,24} The T790M mutation is methionine substitution for threonine at position 790 and is present in >60% of NSCLC cases that develop *EGFR* TKI resistance.²⁵ Osimertinib is a third-generation irreversible TKI that has been approved for T790M-mutant NSCLC.²³ The response we observed to erlotinib was initially substantial, with a 2-log reduction in CA 19-9 level and radiographic PR. However, the development of the T790M mutation ultimately prevented a durable response beyond 280 days. Unfortunately, our patient did not experience a response to osimertinib.

The initial biopsy had an exon 19 deletion in *EGFR* with an MAF of 16%, which, when accounting for both alleles, is assumed to be present in 32% of the sample. The sample was estimated to be <40% tumor and thus the exon 19 deletion was present in nearly all tumor cells. The T790M mutation was initially detected by TaqMan assay, and the MAF cannot be reported by this assay. However, retrospective pyrosequencing by the Yale Clinical Molecular Pathology Laboratory detected an MAF of 27% for T790M, with the sample estimated to be 90% tumor. In contrast to the exon 19 deletion, when accounting for both alleles, T790M would be expected to be present in 49% of tumor cells. In NSCLC, even T790M allelic fractions of <5% have been associated with resistance to first-generation TKIs.²⁶

In T790M-mutated NSCLC, the overall response rate with osimertinib is reported to be 61%, with a disease control rate of 95%.²³ The C797S mutation is the most common mechanism of acquired resistance to third-generation TKIs. However, it is unlikely to play a role in our patient who had primary resistance to osimertinib.²⁷ For T790M-

Table 1. Literature Review of Nonlung Tumors With Activating Mutations in *EGFR* That Have Received Treatment With EGFR TKIs

Tumor Type	N	EGFR Mutation	Treatment	PFS, mo	Reference
Pancreatic adenocarcinoma	1	Exon 19	Capecitabine/erlotinib	>8	Zill et al, ¹⁸ 2015
Pancreatic adenocarcinoma	2	Exon 19	Capecitabine/erlotinib	>3	Kwak et al, ¹⁴ 2006
Ovarian cancer	1	Exon 19	Gefitinib	27	Schilder et al, ¹⁵ 2005
Ovarian cancer (high-grade papillary serous carcinoma)	1	Exon 19	Erlotinib/cetuximab/bevacizumab	4	Wheler et al, ¹⁷ 2013
Parathyroid carcinoma	1	Exon 20	Erlotinib	6	
Carcinoma of parotid gland	1	Exon 20	Erlotinib/cetuximab/bevacizumab	1	
Head and neck (epiglottis)	1	Exon 21	Cetuximab/carboplatin/paclitaxel	3	
Sarcoma (unclassified spindle cell)	1	Exon 19	Erlotinib	2	
Basal cell carcinoma	1	Exon 19	Cetuximab/carboplatin/paclitaxel	7	
			Cetuximab/sirolimus	2	
Cutaneous squamous cell carcinoma	1	Exon 19	Cetuximab/sirolimus	>9	Ganesan et al, ²² 2016

Abbreviations: EGFR, epidermal growth factor receptor; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

mutated tumors, primary resistance to third-generation TKIs is rare and not well described. However, for our patient, several possible mechanisms of primary resistance are possible. One consideration would be T790M heterogeneity among disease sites, but at 8 weeks there were multiple sites of disease progression, including the T790M-positive liver lesion that increased from 2.8 to 4.5 cm. Another more likely explanation would be a simultaneous activation of an *EGFR*-independent process, which includes known alternative mechanisms of *EGFR* resistance such as amplification of *MET* or *HER2*, and mutations in *BRAF* or *PIK3CA*.^{28,29} This process could be present in either all tumor cells or more likely the cells without T790M. The lack of response to osimertinib is disappointing, but our patient’s course reveals that pancreatic exon 19 deletions in *EGFR* not only respond to erlotinib but also follow similar resistance pathways.

Widespread use of precision medicine in PDAC has been constrained for many reasons, including insufficient tumor in available biospecimens, low incidence of actionable genomic lesions, and rapid clinical decline after standard chemotherapy. Despite these challenges, recent experience has shown

that genomic analysis is feasible in most patients with PDAC and can identify actionable mutations.⁴ Our patient’s clinical course highlights the potential clinical benefit of a biomarker-driven targeted therapy in refractory advanced PDAC. Additionally, our analysis supports the observation that, when mutated, the *EGFR* pathway functions similarly across tumor types with conserved mechanisms of resistance. Mutations in *EGFR* remain rare in PDAC, and the mutational landscape is predominantly highlighted by mutations for which targeted therapies are unavailable. However, given the limited treatment options for metastatic PDAC, genomic analysis should be considered for all patients with advanced disease.

Conclusions

In advanced PDAC, treatment options remain extremely limited after first-line chemotherapies are exhausted. This case illustrates the value and potential benefit of a precision medicine strategy. Actionable mutations in *EGFR* can be effectively targeted in PDAC, and appear to follow similar resistance patterns already established in NSCLC.

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