Disease flare after tyrosine kinase inhibitor discontinuation in patients with *EGFR*-mutant lung cancer and acquired resistance to erlotinib or gefitinib – implications for clinical trial design

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Abstract

Purpose: Treatment of patients with oncogene-addicted cancers with tyrosine kinase inhibitors (TKI) is biologically and clinically different than with cytotoxic chemotherapy. We have observed that some patients with *EGFR*-mutant lung cancer and acquired resistance to erlotinib or gefitinib (RECIST progression after initial benefit) have accelerated progression of disease after discontinuation of TKI. To examine this observation and define the course of patients following TKI discontinuation, we systematically evaluated patients enrolled on clinical trials of agents to treat acquired resistance to erlotinib or gefitinib.

Methods: We evaluated patients with *EGFR*-mutant lung cancer who participated in trials for patients with acquired resistance which mandated TKI discontinuation prior to administration of study therapy. Disease flare was defined as hospitalization or death attributable to disease progression during the "washout" period.

Results: Fourteen of 61 patients (23%; 95% CI 14-35%) experienced a disease flare. The median time to disease flare after TKI discontinuation was 8 days (range 3-21). Factors associated with disease flare included shorter time to progression on initial TKI (p=0.002) and the presence of pleural (p=0.03) or CNS disease (p=0.01). There was no association between disease flare and the presence of T790M at the time of acquired resistance.

Conclusion: In patients with *EGFR*-mutant lung cancer and acquired resistance to EGFR TKIs, discontinuation of erlotinib or gefitinib prior to initiation of study treatment is associated with a clinically significant risk of accelerated disease progression. Clinical trials in this patient population must minimize protocol mandated washout periods.

Keywords

EGFR; adenocarcinoma of lung; drug resistance

Statement of Translational Relevance

We systematically evaluated an observed phenomenon of rapid and symptomatic disease progression that occurs in patients with *EGFR*-mutant lung cancer and acquired clinical resistance to gefitinib and/or erlotinib shortly after discontinuation of the EGFR kinase

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inhibitor. By using the standard practice of a mandated drug washout period during clinical trials, we evaluated the disease course and associated clinical and molecular factors of patients enrolled on clinical trials to treat acquired resistance. We found that 23% of patients experienced a symptomatic disease flare, defined as hospitalization and/or death attributable to disease progression after discontinuation of erlotinib or gefitinib but before initiation of study drug. While this analysis has the obvious limitations of a retrospective study, we feel that the risk of disease flare in this patient population is significant enough to merit modification of clinical trial design to abbreviate standard washout periods in trials for patients with *EGFR*-mutant lung cancer and acquired resistance.

Introduction

The treatment of non-small cell lung cancer (NSCLC) has been dramatically altered in the past decade with the identification of somatic gene mutations that underlie tumor initiation and maintenance. *EGFR* mutations were first identified in lung cancer after clinical benefit to EGFR tyrosine kinase inhibitors was observed(1-4). Evaluation of tumor specimens in these patients led to the identification of two common mutations in *EGFR*, the exon 19 deletion and the exon 21 L858R missense mutation, which lead to constitutively activated EGFR kinase readily inhibited by gefitinib and erlotinib.

In patients with NSCLC whose tumors harbor an *EGFR* mutation, first-line TKI therapy is recommended(5-7). Patients who initially benefit from erlotinib or gefitinib and then develop progression of disease, are described as having acquired resistance(8). There is no genotype-directed standard therapy for patients with acquired resistance to erlotinib or gefitinib. Cytotoxic therapies are generally used(9). Studies of second-generation EGFR inhibitors, as well as other strategies, are ongoing.

Even after the development of acquired resistance to gefitinib and/or erlotinib, *EGFR*-mutant lung cancer has a unique biology, with a median post-progression survival of 19 months in patients with an acquired T790M resistance mutation and 12 months in those without an identified T790M, though it is important to note that in the reported series TKI therapy was continued in 91% and 83% of these patients, respectively(10). Despite this remarkable post-progression survival, we have noted that discontinuation of EGFR inhibition causes some patients to experience more rapid progression of symptoms, or a disease flare. Nonetheless, anti-cancer treatment discontinuation is usually mandated as part of the eligibility criteria for enrollment in clinical trials. We used this practice of a trial-mandated erlotinib and gefitinib washout period as an opportunity to estimate the frequency of disease flare upon EGFR inhibitor discontinuation and to evaluate clinical and molecular characteristics that may be associated with disease flare.

Materials and Methods

We identified all patients enrolled in therapeutic clinical trials at our institution for patients with lung cancer who had developed acquired resistance to erlotinib and/or gefitinib. Trials were only included if they mandated discontinuation of the TKI for at least 7 days. Patients were included in this analysis if their tumors harbored a sensitizing *EGFR* mutation (exon 18 point mutation G719X , exon 19 deletion, or exon 21 point mutations L858R and L861Q) and met the consensus criteria for acquired resistance(8). Patients who were enrolled in more than once such clinical trial were evaluated only during the initial washout period. Testing for *EGFR* mutations was as previously described(11, 12).

The primary endpoint of this analysis was frequency of disease flare after discontinuation of TKI, defined as hospitalization or death attributable to disease progression after stopping the

TKI and prior to initiation of study therapy. Hospitalizations due to infection, venous thromboembolism and other non-oncologic issues were not considered a disease flare. Clinical characteristics and disease course were reviewed for all patients under an Institutional Review Board/Privacy Board waiver. Time to progression (TTP) on initial TKI was calculated from date of first TKI until date of physician documented progression. Time on TKI was calculated from date of first TKI until date of discontinuation for trial washout. For patients who had a disease flare, time to flare was calculated from date of TKI discontinuation to date of hospitalization or death. Correlative variables that are binary were evaluated with the Fisher exact test. For time to progression on TKI, distribution plots were compared with Wilcoxon rank tests.

Results

Six clinical trials studying patients with acquired resistance to EGFR TKIs were identified, accruing patients between August of 2005 and January 2011. The 6 trials included in this analysis and the numbers of patients who participated in each trial are included in Figure 1(13-17). Of the 84 patients enrolled in the 6 trials studied, 14 were excluded due to lack of a documented sensitizing mutation in *EGFR*. Seven patients were enrolled in multiple trials (three trials for 2 patients and two trials for 5 patients). These patients were included only during their first washout period. Patient characteristics are presented in Table 1.

Fourteen of the 61 patients included in this analysis (23%, 95% CI 14-35%) had a disease flare (hospitalization or death attributable to disease progression) after discontinuation of the TKI. The median time to disease flare was 8 days (range 3 - 21 days). Only 3 of the 14 patients (21%) continued on the therapeutic trial in which they had enrolled. The clinical characteristics of the 14 patients who had a disease flare are shown in Table 2. Of these, 9 had *EGFR* exon 19 deletions, 1 had two exon 18 point mutations and 4 had exon 21 L858R point mutations. *EGFR* T790M results at the time of acquired resistance were available for 52 patients including 11 of the 14 patients with disease flare. An *EGFR* T790M was mutation found in 6 patients (55%) who experienced a disease flare and 27 patients (59%) who did not.

We compared clinical characteristics in patients who did and did not develop a flare after TKI discontinuation. Patients with disease flare had a shorter time to progression on TKI treatment (median 9 months, range 1-19 months) than patients who did not experience flare (median 15 months, range 5-72 months, p = 0.002) (Figure 2). The time from documentation of acquired resistance to trial enrollment for all patients was a median of 6 months (range 0 – 48 months) and was not different between the groups (p=0.46). In the 30 days prior to TKI discontinuation, there were 4 disease-related hospitalizations, 2 in each group (p=0.2). Flare was associated with the presence of brain or pleural metastases prior to TKI discontinuation (p=0.01 and 0.03, respectively). Flare was not associated with type of *EGFR* sensitizing mutation, presence/absence of T790M, performance status, sex, tobacco use, or specific TKI (Table 3).

Discussion

In this analysis of patients with acquired clinical resistance to EGFR TKI therapy, we observed a 23% flare rate during the EGFR TKI washout period, defined as hospitalization or death attributable to disease progression. After identifying the phenomenon of disease flare in a prior study(14), we had attempted to minimize harm by abbreviating the standard washout periods of 21-28 days to 14 days in more recent trials. Despite this precaution, patients continued to experience flare after a median of only 8 days off TKI. Characteristics associated with development of flare included a shorter time to progression on initial TKI,

preceding symptoms of disease progression, and presence of CNS and pleural disease. We recently reported that when acquired resistance is attributable to a T790M point mutation, disease may follow a more indolent course than clinical resistance without T790M(10). However, in this study there was not a lower rate of disease flare in patients with T790M-mediated acquired resistance. We believe that the rate of rapid disease progression reported here is clinically significant and should alter the design of clinical trials in this patient population.

This analysis has the inherent limitations of a retrospective study, which prevented us from identifying a matched comparison group to study the prevalence of disease flare in the absence of TKI discontinuation. Attempts to model an internal comparison group by comparing the patterns of disease progression within the same patient before and after TKI discontinuation were hampered by incomplete data on some patients prior to enrollment. This cohort was relatively fit in that all patients had a KPS of 70%. Furthermore, the median time from acquired resistance to discontinuation of TKI was 6 months and the hospitalization rate in the 30 days before TKI washout was not significantly different between the patients who experienced a disease flare and those who did not; this supports a causal relationship between TKI discontinuation and disease flare rather than a more aggressive underlying biology in the patients who experienced a disease flare. Due to the high event rate and no discernable difference in groups during the period between development of acquired resistance and trial enrollment, we anticipate that these observations are likely to be replicated if evaluated prospectively, although we do not advocate this as it may lead to an unacceptable risk to patients.

When acquired resistance occurs in oncogene-driven cancers with kinase activation, kinase activation persists or increases despite continued treatment with a kinase inhibitor. However, not every cell is resistant, as demonstrated in gastrointestinal stromal tumors where the resistant and clones can be visualized in a "matrix" of sensitive cells(18). If imatinib is stopped in these patients, growth is accelerated in the sensitive clone resulting in rapid and symptomatic progression that is associated with a PET flare(19). We believe the same mechanism occurs in *EGFR*-mutant lung cancers that have developed acquired resistance to erlotinib or gefitinib(20).

Based on preclinical studies that show *EGFR*-mutant cells made resistant to gefitinib can become sensitive once again by successive passages in the absence of the TKI(21) and clinical observations that after a period of TKI discontinuation patients can respond again to re-institution of the same agents(14), some have suggested withdrawal and retreatment with the same TKI after a "drug holiday" as a strategy to counter acquired resistance. Our data suggest that this approach is not suitable for all patients and that drug holidays can lead to more rapid tumor growth. A more appropriate approach would be to immediately substitute another therapeutic agent or add a new agent to the TKI.

As we believe that oncogene-addiction persists after the development of acquired resistance, clinical trials to investigate alternative treatment strategies are essential. The data presented here suggest that the usual trial-mandated EGFR TKI washout period in this patient population may be associated with an unacceptably high risk of more rapid disease progression prior to initiation of experimental agents. Mandated drug washout periods are designed to prevent interactions between drugs but are often broadly written to include all anti-neoplastic drugs. In early phase studies evaluating the safety and efficacy of erlotinib, the half-life ($t_{1/2}$) was determined to be 8 hours(22). Therefore, in patients with normal hepatic function, a 24-48 hour washout period should be sufficient for drug clearance and will minimize the risk of significant disease flare. Only 1 of 14 patients in the flare group experienced the flare in 3 or fewer days after TKI discontinuation.

Oncogene addiction is a phenomenon recognized in many malignancies. Targeting the downstream effects (especially kinase activation) of these driver-mutations has been a successful strategy in chronic myelogenous leukemia, gastrointestinal stromal tumors, *BRAF*-mutant melanoma, and *ALK*-rearranged and *EGFR*-mutated lung cancer with dramatic and often durable responses(23-26). Gastrointestinal stromal tumors have a unique biology with rapid disease progression when the kinase inhibitor imatinib is removed after prolonged benefit(27). This series describes a similar flare phenomenon in the setting of acquired resistance in *EGFR*-mutant lung cancer when gefitinib or erlotinib are stopped because of radiographic disease progression and we anticipate that similar observations will be made in other oncogene driven malignancies treated with targeted inhibitors. As we investigate better treatments for patients with tumors that have developed acquired resistance to gefitinib and erlotinib, clinical trials should abbreviate trial mandated washout periods to minimize the risk of disease flare upon TKI discontinuation in patients with *EGFR*-mutant lung cancer.

Acknowledgments

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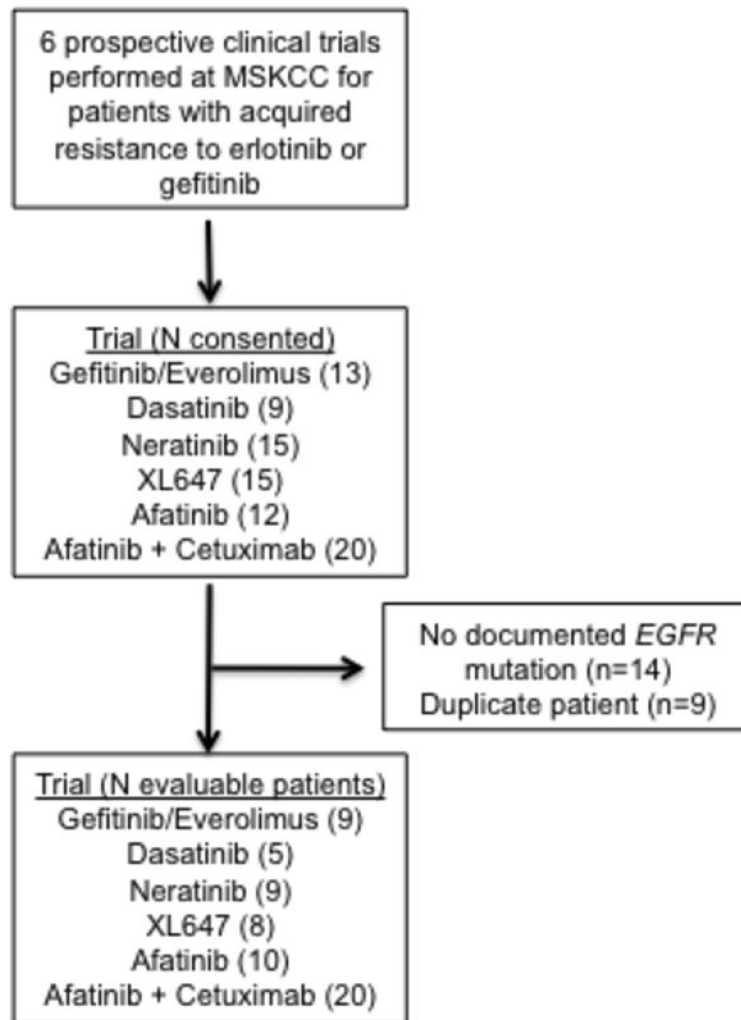
Figure 1.
Trials evaluated

Time to Progression
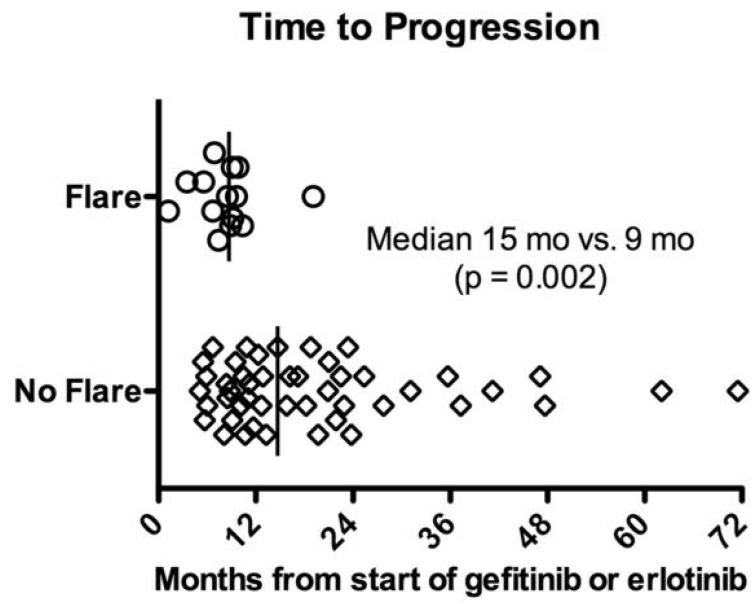
Figure 2.
Time to progression on initial tyrosine kinase inhibitor (TKI) in patients with and without flare after TKI discontinuation

Table 1

Patient characteristics

Characteristic	
Male sex – N (%)	13 (21)
Age at diagnosis in years – Median (range)	58 (26-78)
Smoking Status	
Former/Current	12 (20)
Never (<100 cigarettes lifetime)	49 (80)
EGFR mutation – N (%)	
Exon 19 deletion	41 (67)
Exon 18 E709A and G719A	1 (2)
Exon 21 L858R	19 (31)
Time on gefitinib or erlotinib (months)	
Median (range)	19 (7-78)
Age at enrollment in years – Median (range)	61 (27-80)
Karnofsky Performance Status at enrollment (%)	
90%	13 (21)
80%	37 (61)
70%	11 (18)
Lines of therapy prior to gefitinib/erlotinib (N%)	
0	37 (61)
1	20 (32)
2	4 (7)
Lines of therapy after acquired resistance	
0	41 (67)
1	12 (20)
2+	8 (13)
First-line gefitinib/erlotinib – N (%)	
Single-agent	29 (48)
With chemotherapy	8 (13)
Maintenance after chemo	5 (9)
Gefitinib/erlotinib/Both – N (%)	
Erlotinib	50 (82)
Gefitinib	6 (10)
Gefitinib followed by erlotinib	5 (8)
Acquired resistance to trial enrollment (months)	
Median (range)	6 (0-48)

Table 2

Disease characteristics and course of patients with disease flare after discontinuation of TKI. TKI (tyrosine kinase inhibitor)

Sex & Smoking	*EGFR* mutation	T790M	Sites of Disease	Days off TKI	Description of Flare
47 Female Never smoker	Exon 19 Deletion	No	Pleura Brain Liver	21 days	Progressive liver metatases with liver failure and death
64 Female Never smoker	Exon 19 Deletion	No	Pleura	21 days	Dyspnea
53 Female Never smoker	Exon 19 Deletion	Unknown	Pleura Brain Bone	14 days	CNS progression
60 Female Never smoker	Exon 21 L858R	Unknown	Pleura Brain Bone	7 days	Hypoxia and Bone pain
34 Male Never smoker	Exon 19 Deletion	No	Pleura Brain	11 days	Dyspnea
27 Female Never smoker	Exon 19 Deletion	Unknown	Brain Liver Bone Pericardium	11 days	Bone pain
47 Female Never smoker	Exon 21 L858R	Yes	Pleura	7 days	New leptomeningeal disease
49 Male Never smoker	Exon 19 Deletion	Yes	Bone Liver	7 days	New brain metastases, seizure
61 Female Never smoker	Exon 21 L858R	No	Pleura Brain Liver Peritoneum	3 days	Abdominal pain
45 Female Never smoker	Exon 19 Deletion	Yes	Pleura Bone	8 days	New leptomeningeal carcinomatosis, seizure, death
46 Female Former smoker	Exon 19 Deletion	Yes	Pleura Liver Bone	12 days	Epidural progression
62 Female Never smoker	Exon 19 Deletion	Yes	Pleura Bone Pericardium	8 days	Pericardial tamponade, death
42 Female Never smoker	Exon 18 E709A & G719A	Yes	Pleura Bone	8 days	Acute pleural effusion requiring drainage
67 Female Former smoker	Exon 21 L858R	No	Pleura Brain	8 days	Dyspnea

Table 3

Characteristics associated with flare following discontinuation of TKI. TKI (tyrosine kinase inhibitor)

Clinical Characteristic	Number	% Flare	p-value
Exon 19 deletion	41	22%	1
Exon 21 L858R	19	21%	
T790M	33	18%	0.5
No T790M	19	26%	
First-line TKI alone	29	34%	0.06
First-line chemo	32	13%	
TKI only	20	30%	0.5
Chemo	41	20%	
Symptoms of disease progression	20	40%	0.05
No symptoms	41	15%	
Karnofsky Performance Status 70%	11	36%	0.4
Karnofsky Performance Status 80-90%	50	22%	
CNS involvement	14	50%	0.01
No CNS disease	47	15%	
Bone involvement	31	26%	0.8
No bony disease	30	20%	
Pleural involvement	36	33%	0.03
No pleural disease	25	8%	
Male	13	15%	0.7
Female	48	25%	
Erlotinib	40	33%	0.3
Gefitinib	11	9%	
Current/Former Smoker	12	16%	0.7
Never smoker	49	24%	