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

Jamie E. Chaft, Geoffrey R. Oxnard, Camelia S. Sima, Mark G. Kris, Vincent A. Miller, and Gregory J. Riely

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 that mandated TKI discontinuation before 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.

Conclusions: In patients with EGFR-mutant lung cancer and acquired resistance to epidermal growth factor receptor TKIs, discontinuation of erlotinib or gefitinib before 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.

Clin Cancer Res; 17(19); 6298–303. ©2011 AACR.

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 epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors was observed (1–4). Evaluation of tumor specimens in these patients led to the identification of 2 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 tyrosine kinase inhibitor (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 and 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 postprogression 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 postprogression survival, we have noted that discontinuation of EGFR inhibition causes some patients to experience more rapid progression of symptoms, or a disease flare.
Nonetheless, anticancer 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 deletions, or exon 21 point mutations L858R, and L861Q) and met the consensus criteria for acquired resistance (8). Patients who were enrolled in more than one 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 before initiation of study therapy. Hospitalizations due to infection, venous thromboembolism and other nononcologic 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 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’s 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 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 (3 trials for 2 patients and 2 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% confidence interval (CI): 14–35] had a disease flare (hospitalization or death attributable to disease pro-
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male sex, n (%)</th>
<th>Age at diagnosis in years, median (range)</th>
<th>Smoking status</th>
<th>EGFR mutation, n (%)</th>
<th>Lines of therapy before gefitinib/erlotinib (n%)</th>
<th>Lines of therapy after acquired resistance</th>
<th>First-line gefitinib/erlotinib, n (%)</th>
<th>Acquired resistance to trial enrollment (mo)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>13 (21)</td>
<td>58 (26–78)</td>
<td>Former/current</td>
<td>12 (20)</td>
<td>0 (71)</td>
<td>0 (11)</td>
<td>29 (48)</td>
<td>50 (82)</td>
<td>19 (7–78)</td>
</tr>
<tr>
<td>Age at diagnosis in years, median (range)</td>
<td></td>
<td></td>
<td>Never (≤100 cigarettes lifetime)</td>
<td>49 (80)</td>
<td>1 (2)</td>
<td>4 (7)</td>
<td>120 (20)</td>
<td>60 (10)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td>Exon 19 deletions</td>
<td>41 (67)</td>
<td>1 (2)</td>
<td>2 (7)</td>
<td>41 (67)</td>
<td>50 (82)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>EGFR mutation, n (%)</td>
<td></td>
<td></td>
<td>Exon 18 E709A and G719A</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>4 (7)</td>
<td>12 (20)</td>
<td>60 (10)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Lines of therapy before gefitinib/erlotinib (n%)</td>
<td></td>
<td></td>
<td>Exon 21 L858R</td>
<td>19 (31)</td>
<td>1 (2)</td>
<td>2 (7)</td>
<td>12 (20)</td>
<td>60 (10)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Time on gefitinib or erlotinib (mo)</td>
<td></td>
<td></td>
<td>Med/Short (mo)</td>
<td>19 (7–78)</td>
<td>19 (7–78)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>60 (10)</td>
<td>1 (20)</td>
</tr>
</tbody>
</table>

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 to 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 before enrollment. This cohort was relatively fit in that all patients had a KPS of 70% or more. 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 shown in gastrointestinal stromal tumors where the resistant 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).

On the basis of 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 reinstitution 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 before initiation of experimental agents. Mandated drug washout periods are designed to prevent interactions between drugs but are often broadly written to include all antineoplastic drugs. In early phase studies evaluating the safety and efficacy of erlotinib,
24- to 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.

Disclosure of Potential Conflicts of Interest

G.J. Riely is the consultant and advisory board member of AstraZeneca, Boehringer-Ingelheim. M.G. Kris is the consultant and advisory board member of AstraZeneca, Boehringer-Ingelheim, Pfizer. V.A. Miller is the consultant and advisory board member of Roche, Genentech, OSI.

Grant Support

This work was supported in part by the grants P01-CA129243 (M.G. Kris) and NIH T32 CA009207 (D. Bajorin).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received June 9, 2011; revised August 2, 2011; accepted August 11, 2011; published OnlineFirst Aug 19, 2011.

References

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


Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-11-1468

Cited articles
This article cites 26 articles, 12 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/17/19/6298.full#ref-list-1

Citing articles
This article has been cited by 32 HighWire-hosted articles. Access the articles at:
http://clincancerres.aacrjournals.org/content/17/19/6298.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.