Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR mutant lung cancer: Distinct natural history of patients with tumors harboring the T790M mutation

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Running head: Distinct natural history associated with T790M

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Translational Significance

This analysis evaluates whether there is prognostic significance to the T790M mutation in patients with EGFR mutant lung cancer who have developed acquired resistance EGFR tyrosine kinase inhibitors (TKIs) like erlotinib. Preclinical data have suggested that T790M mutant cell lines have indolent growth, but such an indolent behavior has not been previously demonstrated clinically. In this analysis, we find that patients with T790M-mediated acquired resistance have relatively favorable progression characteristics and clinical outcomes, suggesting that this mutation identifies a subset of cancers with a distinct biology. Our findings indicate that T790M may be an important prognostic and mechanistic biomarker in patients with acquired resistance, and mutation status should be routinely determined in patients enrolling in clinical trials for acquired resistance.
Abstract:

**Purpose:** Patients with EGFR-mutant lung adenocarcinoma develop acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) after a median of 10-16 months. In half of these cases a second EGFR mutation, T790M, underlies acquired resistance. We undertook this study to examine the clinical course of patients harboring the T790M mutation following progression on TKI.

**Experimental design:** EGFR-mutant lung cancer patients with acquired resistance to EGFR TKIs were identified as part of a prospective re-biopsy protocol where post-progression tumor specimens were collected for molecular analysis. Post-progression survival and characteristics of disease progression were compared in patients with and without T790M.

**Results:** We identified T790M in the initial re-biopsy specimens from 58/93 patients (62%, 95% confidence interval 52%-72%). T790M was more common in biopsies of lung/pleura tissue and lymph nodes than in more distant sites (p=0.014). Median post-progression survival was 16 months (interquartile range 9-29 months); patients with T790M had a significantly longer post-progression survival (p=0.036). Patients without T790M more often progressed in a previously uninvolved organ system (p=0.014) and exhibited a poorer performance status at time of progression (p=0.007).

**Conclusions:** Among patients with acquired resistance to EGFR TKIs, the presence of T790M defines a clinical subset with a relatively favorable prognosis and more indolent progression. Knowledge of T790M status is therefore important for the clinical care of these patients as well as for the optimal design and interpretation of clinical trials in this setting.
Introduction

The identification of EGFR sensitizing mutations in a subset of patients with lung adenocarcinoma has transformed the management of non-small cell lung cancer (NSCLC). This molecular subtype of lung cancer, diagnosed in approximately 20,000 patients in the United States each year, is the largest in a small group of cancers (including chronic myelogenous leukemia and gastrointestinal stromal tumor) which have been found to have profound sensitivity to single agent tyrosine kinase inhibitors (TKIs). Multiple studies have shown that patients with EGFR mutant lung cancer have an approximately 70% RECIST response rate to EGFR TKI's (1-4). Prospective analyses have demonstrated that presence of an EGFR sensitizing mutation is the biomarker most strongly associated with progression free survival benefit from first-line EGFR TKI treatment over chemotherapy (3, 5, 6).

Patients with EGFR mutant lung adenocarcinoma develop progression of disease on TKI therapy after a median of 10-16 months (1, 3, 7). This condition has been described as "acquired resistance" to TKI, and the complexity of trial design and interpretation in this setting has led to recent publication of consensus clinical criteria for patient eligibility (8-11). Several groups studying the molecular biology of acquired resistance have found that at least 50% of cases are attributable to a secondary mutation, T790M, in exon 20 of EGFR (12-14). This mutation is felt to change the relative affinity of the mutant receptor in favor of ATP, largely abrogating the effect of the TKI (15). The T790M mutation has also occasionally been detected in tumor specimens from patients with no prior exposure to EGFR TKIs (3, 16-19), though the prevalence of "baseline T790M" can vary depending on the detection method employed.
While the detection of T790M in baseline specimens has been associated with a poorer outcome on TKI therapy (18), the association between T790M-related acquired resistance and clinical outcomes has not been systematically explored. Preclinical data have shown that EGFR-mutant cell lines that acquire the T790M mutation have a more indolent growth when compared to parental cell lines (J. Chmielecki, et al, submitted)(20), which could translate in vivo into a more indolent natural history. Based upon this preclinical finding, we tested the hypothesis that patients with EGFR mutant tumors and T790-mediated acquired resistance to EGFR TKIs would have a favorable natural history when compared to patients with acquired resistance lacking the T790M mutation.

Methods

Through a prospective re-biopsy protocol, consecutive patients with advanced EGFR-mutant lung adenocarcinoma were identified who had acquired resistance to EGFR TKI. Patients must have had response or durable stable disease (>6 months) on TKI followed by progression while receiving TKI. Eligibility was based upon consensus criteria (8), with the exception that patients who received a TKI in combination with chemotherapy were considered eligible if their tumor harbored an EGFR mutation. Patients were also allowed to receive subsequent therapies in the interval since progression on TKI. Beginning in August 2004 patients with lesions amenable to biopsy were enrolled on a clinical trial to biopsy a growing site of disease (21). Additional patients from this period were included in the analysis if they possessed post-progression biopsy material obtained during a clinically indicated procedure, so long as they consented to a separate clinical trial allowing correlative tissue analyses.
Specimens were tested for the presence of an EGFR sensitizing mutation using a PCR based assay previously described (22). Samples not found to harbor an EGFR sensitizing mutation were excluded from this analysis. Testing for the T790M mutation was then performed using standard methodologies (12, 23). For cases where additional tumor DNA was available, highly-sensitive testing was also performed using sequencing augmented by a locked-nucleic-acid (LNA), which suppresses amplification of the wild-type allele and allows detection of T790M when present in as little as 0.1% of DNA (M. E. Arcila, et al, submitted)(23). Patients were classified as “T790M-positive” or “T790M–negative” based upon whether T790M was detected in their first post-progression biopsy specimen that was adequate for molecular testing. For patients with adequate tissue available, MET amplification was tested by fluorescence in situ hybridization (FISH)(24); cases were considered amplified if the ratio of MET to CEP7 was greater than 2:1.

Patient charts were retrospectively reviewed, in an IRB approved fashion, to summarize potentially relevant clinical characteristics and disease course. The association between the prevalence of the T790M mutation and clinical factors was tested using a Fisher’s exact test. The date of progression was defined clinically based on (1) sufficient growth of tumor in a known site of disease to make a clinician discuss alteration of therapy as documented in the patient’s medical chart and/or (2) imaging showing a new site of metastatic disease. Progression was identified as involving a new metastatic organ system if new metastases were identified within one week of date of progression. For the time to new metastasis analysis, the date of a new metastasis was defined as the date of the scan that documented metastatic involvement of a new organ system; patients without new metastases were censored at the date of last imaging evaluation. For survival analyses, patients were censored at date last...
known alive. All time-to-event outcomes were estimated using Kaplan-Meier method and compared across groups using log-rank testing (for univariate analysis) and Cox proportional hazards model (for multivariate analysis).

Results

We identified 127 patients with EGFR-mutant lung cancer and acquired resistance meeting eligibility criteria; 115 consented to the re-biopsy protocol while 12 had consented to a separate protocol allowing correlative tissue analyses. Of these patients, 107 (84%) had adequate post-progression tissue available for complete mutation analysis. We then excluded 4 patients because they began an EGFR TKI as an adjuvant therapy while having no evidence of disease, 6 patients because they initially received an investigational EGFR TKI with known additional targets, and 4 patients who had progression in the CNS only, a condition which has been described to be sensitive to TKIs when given in higher doses (25, 26). The remaining 93 patients comprised our group for analysis. To evaluate for selection bias, we compared our cohort to a reference cohort of all EGFR-mutant lung cancer patients with advanced disease treated at our institution (287 patients)(27), and found no difference in median survival from date of advanced disease (40 vs. 37 months, p=0.24, Supplementary Figure 1).

Characteristics of the 93 patients are outlined in Table 1. Patients began TKI between February 1999 and August 2009 and developed progression between August 2003 and November 2009. 90 of 93 biopsies (97%) were performed on sites of growing disease. The median interval between date of progression and date of re-biopsy was 7 weeks (interquartile range 3-21 weeks). 58 patients (62%, 95% CI 52%-72%) had the T790M mutation detected in their initial post-progression biopsy; 35 patients (38%, 95% CI 28%-47%) were found to be
T790M negative. 77% of patients received erlotinib or gefitinib as part of their initial therapy. We continued EGFR TKI therapy following disease progression in addition to subsequent therapies in 87% of patients (9). The T790M mutation was found at similar frequencies across multiple different patient characteristics (Table 1), although the prevalence was higher in lung/pleura and lymph node specimens than in more distant sites (p=0.014).

The median follow-up was 13 months following disease progression and 67% of patients had died. Median post-progression survival for the entire cohort was 16 months (interquartile range 9-29 months); comparison of post-progression survival from patients with and without T790M is shown in Figure 1A. Patients with T790M had a median post-progression survival of 19 months, longer than the 12 month median post-progression survival of patients without T790M (p=0.036). Characteristics of disease progression were compared in patients with T790M and without (Table 2). Patients with T790M were more likely to progress in an existing site of disease rather than a new organ system (p=0.010). Analysis of time to development of metastasis beginning with date of progression found earlier development of new metastatic organ system involvement in patients without T790M (p=0.008, Figure 1B). Patients without T790M were also found to have a lower Karnofsky Performance Status at time of progression (p=0.007). No differences in post-progression treatment were found in the two groups (Table 2). In multivariate analysis, there was no additional difference in post-progression survival based upon T790M status when controlling for performance status and presence of new metastatic disease at progression (p=0.27).

To determine whether the difference in clinical course after progression was related to a different disease course prior to progression on TKI, we compared time to progression (TTP) on TKI in patients with and without T790M. This analysis relies on the hypothesis that the
mechanistic and biologic basis of resistance to therapy is a phenomenon that begins early in the course of treatment and thus can influence disease course long before clinical evidence of progression. Patients who developed T790M had a median TTP of 14 months, which was not significantly different from the median TTP of 11 months in patients who did not develop T790M (p=0.10). Because it can be challenging to determine a specific “date of progression” in patients who have indolent progression on therapy, we performed an exploratory analysis to evaluate the difference in overall survival from the beginning of TKI therapy in patients with and without T790M. While this analysis could be biased because (1) it studies only the selected group of patients who were re-biopsied and (2) patient enrollment occurred after development of progression, it does allow a time-to-event analysis where the start date (start of TKI treatment) and end date (date of death) are more firmly known. Considering these limitations, we found a significant difference in survival between the two sub-groups, with a median survival of 39 months in patients who develop T790M and 26 months in patients who do not (p=0.007, Supplementary Figure 2).

There were adequate MET FISH results for 38 of the 93 patients (41%). Four patients (11%, 95% CI 3%-25%) were found to have MET amplification, a proportion that is lower than previously described (21%-22%) but the difference was not statistically significant (p=0.11)(24, 28). Three of the four patients additionally harbored T790M, including the one patient found to have high level amplification (MET:CEP7 ratio > 8). The small number of patients with MET amplification precluded meaningful outcome analyses in this subset.

Discussion
Patients with EGFR-mutant lung cancer have a prolonged survival compared to the median survival of 12 months commonly reported for patients with advanced NSCLC. While this may in part be due to durable responses to EGFR TKIs, it also is likely that these cancers have a distinct biology from that of EGFR wild-type lung cancers, with greater chemosensitivity and better surgical outcomes. However, this remains a heterogeneous population: some patients with EGFR-mutant lung cancer do poorly after an initial response to TKI while others can live for many years despite advanced disease. Our data suggest that detection of the T790M mutation after progression on TKI identifies a subset of EGFR-mutant lung cancer with a distinct natural history and longer survival, which is consistent with preclinical data showing that EGFR-mutant cell lines that acquire the T790M mutation display indolent growth. If verified prospectively, the T790M mutation would be one of the first acquired molecular biomarkers with prognostic value in solid tumor oncology.

Our data suggest that patients with and without T790M after progression on TKI have very different clinical features of progression, likely driven by their different genotypes. The absence of T790M after progression, likely indicating some “other” resistance mechanism, is associated with earlier development of new metastatic sites of disease and a poorer performance status, contributing to the shorter survival of these patients. Alternatively, T790M-mediated resistance is more likely to occur in an existing site of disease, and has also been found to be associated with indolent disease growth (J. Chmielecki, et al, submitted), characteristics that may explain the longer survival of these patients. Importantly, the vast majority of patients in our dataset were maintained on chronic EGFR TKI therapy after developing resistance in order to prevent growth of TKI-sensitive clones, in addition to subsequent cytotoxic therapies intended to treat the subset of resistant clones.
is not standard practice at most institutions, we believe this strategy may help maintain the indolent characteristics of T790M-associated progression, though it may make our findings difficult to replicate with patient cohorts in which TKI was routinely discontinued upon progression.

The existence of two biologic subtypes of acquired resistance has important implications for clinical trials performed in this setting (9-11), as these two populations likely require distinct treatment approaches. For example, T790M positive patients may be more likely to maintain dependence on the EGFR signaling axis, (31) and thus may benefit from newer strategies targeting EGFR and its signaling pathway (32, 33). This possible role for T790M at resistance as a predictive or prognostic biomarker is complicated by the need for re-biopsy to obtain tumor DNA, a strategy which can be logistically challenging, though we and others have found it feasible (21, 34-36). Technologies allowing minimally invasive determination of T790M status from peripheral blood specimens or cytologic specimens are in development and may simplify this process (18, 37, 38).

For patients without T790M, given their poorer prognosis, it is extremely important that we develop a better understanding of the molecular mechanisms of TKI resistance. MET amplification has been identified as one alternate mechanism of acquired resistance (24, 28), however in the subset of our cohort tested by FISH the prevalence was only 11% (with a single case of high level amplification). Alternate pathways of TKI resistance, of which several have been hypothesized (39), are actively being investigated by multiple groups using high throughput mutation testing, siRNA screens, and gene expression microarray analysis.

The positive prognostic implications of T790M in the acquired resistance setting differ from its negative prognostic role prior to treatment with TKI. (18, 40). In pretreatment EGFR
mutant lung cancers, the reported prevalence of “de novo” T790M has varied wildly (1% to 38%)(3, 17, 18, 40, 41), with the upper end of this range possibly reflecting false positive results with some T790M assays.‡ In the pretreatment setting, patients with no T790M detected would be expected to do better because they harbor only a sensitizing mutation and have not yet acquired a resistance mutation (16-18). In contrast, patients who are “T790M negative” in the resistant setting must harbor some other mechanism of resistance, leading to their poorer prognosis. Note that in our analysis we included only patients who demonstrated a clinical benefit on TKI, therefore patients with a preexisting de novo T790M mutation and disease refractory to TKI treatment would not be included in our cohort. Analysis is ongoing to determine whether patients harboring the T790M after acquired resistance additionally harbor low levels pretreatment; however, no such cases have yet been identified in our cohort (M. E. Arcila, et al, submitted)(42).

One possible limitation of our data is that only a subset of all EGFR-mutant lung cancer patients had biopsy tissue available for molecular analysis after progression on TKI, leading to the exclusion of patients without adequate biopsies. One could hypothesize that poor-prognosis patients would be unable to undergo re-biopsy and would be left out of our analysis, skewing our results. For example, only 25% of our cohort harbored EGFR exon 21 mutations, rather than the expected 40% (1, 3), and these types of mutations have previously been found to be associated with poorer outcomes (2, 43). However, when we compared our cohort to a reference cohort of all EGFR-mutant lung cancer patients treated at the institution we found no difference in median survival from date of advanced disease (Supplementary Figure 1)(27). We therefore believe that our sample accurately represents patients with EGFR-mutant lung cancer treated with erlotinib or gefitinib.
Because of the unique patient population analyzed in this study, accrual and analysis occurred over several years during which time molecular testing techniques have evolved. Initial testing techniques employing direct sequencing and fragment analysis detect mutant clones when present in at least 10-20% of DNA studied. With these techniques, false negative results can occur when specimens contain significant amounts of stromal or inflammatory tissue. Our current testing mechanism, using direct sequencing augmented by a locked nucleic acid (LNA) which inhibits wild-type DNA amplification, is able to detect T790M when present in as little as 0.1% of DNA studied, significantly improving sensitivity of testing (M. E. Arcila, et al, submitted)(23, 42). This may explain why we have found a somewhat higher prevalence of T790M than has previously been reported (12, 35).

In conclusion, we find that patients with acquired resistance to gefitinib and erlotinib harboring the T790M mutation have a distinct natural history, and that this mutation identifies a distinct subset of patients with a longer survival after progression and later development of new metastases. Our data suggest that knowledge of T790M status is important for the clinical care of these patients as well as for the optimal design and interpretation of clinical trials in this setting. A better understanding of the biologic mechanisms of non-T790M-mediated acquired resistance is needed to develop treatments for this poorer prognosis population.
Footnote:

Table 1: Patient characteristics and T790M prevalence

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (% total)</th>
<th>Percent with T790M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33 (35%)</td>
<td>64% (p=1)</td>
</tr>
<tr>
<td>Female</td>
<td>60 (65%)</td>
<td>62%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>17 (18%)</td>
<td>59% (p=0.79)</td>
</tr>
<tr>
<td>Non-Asian</td>
<td>76 (82%)</td>
<td>63%</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>61 (66%)</td>
<td>61% (p=0.66)</td>
</tr>
<tr>
<td>Former/current smoker</td>
<td>32 (34%)</td>
<td>66%</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV at diagnosis</td>
<td>71 (76%)</td>
<td>61% (p=0.62)</td>
</tr>
<tr>
<td>Recurrent</td>
<td>22 (24%)</td>
<td>68%</td>
</tr>
<tr>
<td>EGFR sensitizing mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 19 deletion</td>
<td>70 (75%)</td>
<td>63% (p=1)</td>
</tr>
<tr>
<td>Exon 21 point mutation</td>
<td>23 (25%)</td>
<td>61%</td>
</tr>
<tr>
<td>Initial TKI received</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>64 (69%)</td>
<td>66% (p=0.36)</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>29 (31%)</td>
<td>55%</td>
</tr>
<tr>
<td>Line of treatment with TKI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st-line/maintenance</td>
<td>72 (77%)</td>
<td>64% (p=0.13)</td>
</tr>
<tr>
<td>2nd-line</td>
<td>11 (12%)</td>
<td>36%</td>
</tr>
<tr>
<td>3rd-line or later</td>
<td>10 (11%)</td>
<td>80%</td>
</tr>
<tr>
<td>Site of biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung/pleura</td>
<td>67 (72%)</td>
<td>66% (p=0.014)</td>
</tr>
<tr>
<td>Lymph node</td>
<td>8 (9%)</td>
<td>75%</td>
</tr>
<tr>
<td>Other*</td>
<td>18 (19%)</td>
<td>44%</td>
</tr>
</tbody>
</table>

*Liver (6), bone (4), brain (3), adrenal (2), uterine cervix, skin, peritoneum

TKI: tyrosine kinase inhibitor
Table 2: Survival and progression characteristics as a function of T790M mutation status

<table>
<thead>
<tr>
<th></th>
<th>T790M positive</th>
<th>T790M negative</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=58</td>
<td>N=35</td>
<td></td>
</tr>
<tr>
<td>Median post-progression survival, months</td>
<td>19 (16-24)</td>
<td>12 (8-17)</td>
<td>0.036</td>
</tr>
<tr>
<td>KPS at progression: 80-90%</td>
<td>53 (91%)</td>
<td>26 (74%)</td>
<td>0.007</td>
</tr>
<tr>
<td>60-70%</td>
<td>5 (9%)</td>
<td>4 (11%)</td>
<td></td>
</tr>
<tr>
<td>30-50%</td>
<td>0 (0%)</td>
<td>5 (14%)</td>
<td></td>
</tr>
<tr>
<td>KPS at progression: 60-70%</td>
<td>53 (91%)</td>
<td>26 (74%)</td>
<td>0.007</td>
</tr>
<tr>
<td>30-50%</td>
<td>5 (9%)</td>
<td>4 (11%)</td>
<td></td>
</tr>
<tr>
<td>Site of disease progression:</td>
<td>52 (90%)</td>
<td>24 (69%)</td>
<td>0.014</td>
</tr>
<tr>
<td>New metastatic organ system involved</td>
<td>6 (10%)</td>
<td>11 (31%)</td>
<td></td>
</tr>
<tr>
<td>Existing organ only</td>
<td>52 (90%)</td>
<td>24 (69%)</td>
<td></td>
</tr>
<tr>
<td>Median time from progression to new metastatic organ involvement, months*</td>
<td>14 (8-18)</td>
<td>4 (1-9)</td>
<td>0.008</td>
</tr>
<tr>
<td>TKI continued after progression: Yes</td>
<td>53 (91%)</td>
<td>29 (83%)</td>
<td>0.32</td>
</tr>
<tr>
<td>No</td>
<td>5 (9%)</td>
<td>6 (17%)</td>
<td></td>
</tr>
<tr>
<td>Treated with chemotherapy subsequently: Yes</td>
<td>47 (81%)</td>
<td>35 (71%)</td>
<td>0.31</td>
</tr>
<tr>
<td>No</td>
<td>11 (19%)</td>
<td>10 (29%)</td>
<td></td>
</tr>
<tr>
<td>Treated on clinical trial subsequently: Yes</td>
<td>28 (48%)</td>
<td>13 (37%)</td>
<td>0.39</td>
</tr>
<tr>
<td>No</td>
<td>30 (52%)</td>
<td>22 (63%)</td>
<td></td>
</tr>
</tbody>
</table>

*See methods for detailed definition
KPS: Karnofsky performance status, TKI: tyrosine kinase inhibitor
Figure 1: Post-progression survival (A) and time from progression until new metastasis (B), depending on T790M mutation status.

Supplementary Figure 1: Survival from date of advanced disease, comparing cohort studied to full cohort of patients with advanced EGFR-mutant lung cancer at our institution.(27)

Supplementary Figure 2: Exploratory analysis of overall survival from start of tyrosine kinase inhibitor in patients with and without T790M.
References

11. Johnson ML, Riely GJ, Rizvi NA, et al. Phase II trial of dasatinib for patients demonstrating acquired resistance to treatment with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) erlotinib (E) or gefitinib (G). J Thor Oncol 2009;4: S689.


A. Post-progression survival

- T790M pos
- T790M neg

p=0.036

Number at risk:
- T790M pos: 58, 41, 12, 7, 1, 1, 0
- T790M neg: 35, 16, 7, 3, 2, 0, 0

B. Time to new metastasis

- T790M pos
- T790M neg

p=0.008

Number at risk:
- T790M pos: 58, 23, 7, 5, 1, 0, 0
- T790M neg: 35, 8, 2, 2, 2, 0, 0
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