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Patterns of Initial and Intracranial Failure in Metastatic EGFR-mutant Non-Small Cell Lung Cancer Treated with Erlotinib

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Abstract

Objectives—Patients with metastatic EGFR-mutant (mEGFRmt) NSCLC have favorable survival when treated with erlotinib. We hypothesized that treatment failure in most patients is limited to initial sites of disease, in which case incorporating local therapy such as radiation might further delay progression. We therefore analyzed patterns and predictors of failure in a large cohort of such patients.

Materials and Methods—We reviewed 189 patients treated with erlotinib for mEGFRmt NSCLC. We classified first pattern of failure as involving initial sites only (ISF), new sites only (NSF), or the combination (CSF), and used competing-risks regression to identify factors associated with ISF, progression and overall survival (OS). We also separately analyzed intracranial and intrathoracic failure.

Results—Of 171 patients who progressed, 103 (60.2%) had ISF, 30 (17.5%) had NSF, and 38 (22.2%) had CSF. Younger age and lack of initial CNS involvement independently correlated with ISF, with a trend for higher T and N stage. Higher T and N stage was also a significant predictor of progression. Factors predicting shorter OS were female gender, weight loss, initial intracranial involvement, and 4 extracranial metastases. Intrathoracic progression was a component of first failure in 61%, and three-year cumulative incidence of brain metastasis was 30%.

Conclusion—The main pattern of progression in mEGFRmt NSCLC on erlotinib is in the initial sites of disease. Younger patients and those without brain involvement are particularly likely to develop ISF. This suggests a role for incorporating local therapy into treatment of selected patients with mEGFRmt NSCLC.

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1 Introduction

Given the effectiveness of the tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib, patients with metastatic non-small cell lung cancer (NSCLC) harboring activating mutations in the epidermal growth factor receptor (EGFRmt) have a remarkably long natural history.¹⁻⁴ Though such patients eventually still experience disease progression, their relatively long survival raises the question of whether local therapy such as radiation might prolong progression-free or even overall survival in some of these patients. A benefit for local therapy seems most likely for patients with oligometastatic disease (often defined as five or fewer total lesions) for whom local therapy to all sites is often feasible, and whose prognosis has been theorized to be better than those with florid metastatic disease.

While interest in local ablative therapy for oligometastatic disease has increased tremendously in recent years, the paucity of randomized evidence underscores the need for caution and for prospective trials, as highlighted in several recent reviews.⁵⁻⁷ In the case of oligometastatic NSCLC, multiple studies are underway to evaluate this question in molecularly unselected patients: the SABR-COMET trial will test stereotactic ablative radiotherapy (SABR) in treating oligometastatic recurrence of an otherwise controlled solid primary tumor, though entry criteria are not limited specifically to lung primary tumors; and another phase II study at MD Anderson Cancer Center will assess local consolidative therapy (either surgery or radiotherapy) following chemotherapy for patients with NSCLC with one to three metastases, as well as several other similar studies.⁸⁻¹¹ Finally, the randomized phase III SARON trial will evaluate the addition of definitive radiotherapy to standard chemotherapy in oligometastatic NSCLC patients limited to 3 metastases.¹²

However, such studies of local therapy in oligometastatic disease include a variety of histologies, or do not utilize molecular selection to enhance the underlying probability that patients will have prolonged natural history and a tendency to fail in initially involved sites. Molecularly-selected EGFRmt patients treated with erlotinib represent a particularly promising population for local therapy, but we currently lack a thorough understanding of the pattern of disease progression in these patients. Knowing whether these patients first progress only in their initial sites of disease or in new sites, and identifying predictive factors for either pattern, would not only aid in understanding what sort of surveillance such patients might require, but also in identifying potential subsets that might benefit from early incorporation of local therapy. Though several small reports of oligometastatic progression of oncogene-addicted NSCLC treated with local therapy have shown promising results,¹³⁻¹⁵ only two studies to our knowledge have evaluated the pattern of failure in metastatic patients treated with TKIs—one from a group of molecularly unselected patients and one from a relatively small set of EGFRmt patients treated with TKI.^{16, 17} In both, half or more of the patients had progression limited to their initial sites of disease. Using a larger cohort of molecularly-selected EGFRmt patients treated with erlotinib, we sought to further characterize the frequency with which such patients progress in their initial sites of disease, and identify potential subsets of patients most likely to exhibit this pattern and therefore, potentially benefit from early local therapy. As disease progression in the CNS (typically, in the brain) is also a common pattern of failure in NSCLC with different clinical and treatment paradigms, we also performed a separate, novel analysis of CNS failure and its predictors.

2. Materials and Methods

2.1 Patients

All new patients seen at our institution from 2004 to 2013 were reviewed to identify eligible patients. Eligibility criteria included initial presentation with biopsy-confirmed NSCLC with at least one metastatic site according to the American Joint Committee on Cancer 7th edition, and with pathological molecular testing to confirm the presence of a sensitizing EGFR mutation. We collected baseline variables such as age at diagnosis, sex, stage at diagnosis, smoking history, baseline performance status, type of EGFR mutation, number and size of initial metastases on pretreatment imaging, prior chemotherapy, and upfront local therapy. There was no selection limitation on therapies prior to erlotinib.

Patients who developed metastatic disease only after initial treatment for Stage I–III disease were excluded. Positron-emission tomography (PET) imaging was performed for 79% of all patients as part of the initial staging workup. All patients were treated with erlotinib and followed at our institution, but could have received other first-line systemic therapy, as well as upfront local therapy with either radiotherapy or surgery, prior to erlotinib initiation at the discretion of the treating physician. For our analysis of brain failure patterns, we studied a subset of metastatic patients who had no evidence of upfront brain involvement based on either CT or MRI.

2.2 Mutational analysis

Mutation analysis was conducted by extracting DNA and identifying EGFR exon 19 deletions and exon 21 L858R mutations by standard sequencing, fragment analysis, or both, as previously described. Beginning in January 2009, 92 specific point mutations in multiple genes were identified by use of a mass spectrometry–based mutation profiling assay (Sequenom, San Diego, CA).^{18–20}

2.3 Pattern of failure

Failure was identified via review of follow-up radiological imaging with CT, MRI, or PET after initiation of erlotinib. Eligible patients must have had at least one available imaging report after initiation of erlotinib. In general, imaging studies were obtained every two to four months for patients on maintenance erlotinib therapy. We characterized the pattern of first documented failure as follows: initial-site failure (ISF), new-site failure (NSF), or combined-site failure (CSF). ISF was defined as first failure limited to existing sites of primary or metastatic disease, NSF as first failure arising only in previously uninvolved sites, and CSF as first failure involving both existing and new sites of disease. The sites and date of first failure were recorded. Progression or metastasis within the CNS was not incorporated in the primary analysis of failure pattern, and was analyzed separately. Furthermore, we also assessed whether and when patients progressed in their primary intrathoracic disease sites at any point in their history.

2.4 Statistics

Descriptive summaries of all patient factors were used, including frequencies, percentages, medians, and ranges. There were five endpoints of interest: ISF, intrathoracic progression,

progression defined as ISF, NSF, or CSF, brain metastasis (BM), and overall survival (OS). Competing-risk methods were used to evaluate all endpoints except OS. A cumulative incidence function was used to estimate the probability of the event of interest, where death without the event was treated as a competing risk. For ISF, NSF and CSF were also considered competing risks. Differences in cumulative incidence rate (CIR) between groups were assessed using Gray's method for univariate analyses (UVA). The Fine and Gray method was used for multivariate analyses (MVA). The Kaplan-Meier method was used to estimate OS, and Cox proportional hazards models were used for UVA and MVA. Patients who were still alive and did not experience the event of interest during the study period were censored at the date of last available follow-up. Clinical factors including gender, age, performance status, T and N stage, number and sites of metastatic lesions, initial weight loss, and EGFR mutation type were included in UVA, and factors with $p < 0.20$ in UVA were included in MVA. Statistical significance for all analyses was two-sided and used a 5% significance level ($p < 0.05$). Statistical analyses were performed using R (version 3.2.0; R Development Core Team) with the "survival" and "cmprsk" packages.

3. Results

3.1 Patients

Between 2004 and 2013, 189 patients with metastatic EGFRmt NSCLC met the eligibility criteria and were analyzed. Clinical and baseline characteristics are shown in Table 1. Median age for all patients was 60 years. Two-thirds of patients were non-smokers, 70% were female, and 80% had intrathoracic stage III disease (i.e. T4 or N2-3 disease). The predominant EGFR mutation was an in-frame deletion of exon 19, but a third of patients had an exon 21 L858R deletion, and a small minority had other mutations. At presentation, the majority of patients had four or more total metastases across at least two distinct extracranial metastatic sites (i.e. bone, adrenal, liver, etc). Forty-three patients (22.6%) had received conventional systemic therapy prior to erlotinib initiation. Median time to erlotinib initiation was 43 days from the date of diagnosis.

In a subset of 111 patients with metastatic disease without initial CNS involvement, patient characteristics were comparable to the whole cohort, though a slightly larger proportion had 1–3 total metastases at presentation and only one extracranial metastatic site (Table 1). In patients who presented initially *with* CNS involvement, 32 (41.5%) had upfront initial CNS-directed local treatment prior to erlotinib initiation. Of this group that was treated, 17 underwent whole brain RT, 11 underwent stereotactic RT and 4 had surgical resection.

3.2 Pattern of failure

Over a median follow-up period of 25 months, 103 patients (60.2% of all patients experiencing failure) experienced ISF, 30 (17.5%) NSF, 38 (22.2%) CSF, and 6 death without apparent failure. In the entire cohort, the pattern of failure was predominantly ISF, with a cumulative incidence of ISF of 52% at 24 months (compared with 17% CSF, 12% ISF and 3% death without failure; Figure 1). On UVA, younger age (continuous; HR=1.02, $p=0.014$) and age ≥ 70 (HR=2.01, $p=0.015$) were associated with ISF, with a trend for increasing intrathoracic stage also being associated with ISF (HR=1.55, $p=0.091$). On MVA,

younger age (continuous; HR=1.02, $p=0.035$) and lack of initial CNS involvement both (HR=1.60, $p=0.026$) both remained independently associated with ISF (Table 2).

Intrathoracic primary disease progression was a component of first non-CNS failure for 60% ($n=103$) of patients who progressed, and was the only site of first non-CNS failure in 29% ($n=50$) of patients who progressed. However, we did not identify any independent predictors of intrathoracic progression. Furthermore, of patients that did not have intrathoracic progression as part of first non-CNS failure ($n=85$), 29% ($n=25$) did eventually progress in their intrathoracic sites at a later time following their first non-CNS failure.

Removing death as a competing outcome to identify predictors of any failure, we found younger age, increasing intrathoracic stage, and a greater number of extracranial metastases to be associated with any failure on UVA (See online supplement). On MVA, increasing local stage remained as an independent predictor of any failure (Local stage IIIA/IIIB vs. I/II, HR=1.75, $p=0.026$).

3.3 Intracranial failure

Of the total cohort, 111 patients initially presented with metastatic disease without CNS involvement. In this group, median overall survival (OS) was 33.8 months, and the two-year cumulative incidence of brain metastasis (BM) was 14.9%; by three years, the cumulative incidence was 30.4% (Figure 2A). On UVA, only EGFR mutation status was associated with the risk of BM, with patients with exon 21 L858R mutations having nearly twice the risk of BM as those with exon 19 deletions (HR 1.93, 95% CI 1.05–3.57, $p=0.035$), and this retained borderline significance on MVA with HR=1.82, 95% CI 0.99–3.36, $p=0.055$. The two-year cumulative incidence of BM in those with exon 19 deletions was 10.6% versus 23.2% in those with the exon 21 L858R mutation (Figure 2B).

Within this set of patients that presented without initial CNS involvement, CNS failure preceded extracranial failure in four patients (10.5% of the 38 that had eventual CNS failure, 4% of the 102 patients that experienced *any CNS or non-CNS* failure). Two patients had CNS failure detected synchronously with extracranial progression. Lastly, in the remaining 32 patients with CNS failure (84% of patients with CNS failure, 31% of those with *any CNS or non-CNS* failure), CNS failure followed extracranial failure, with a median time to CNS failure of 13.1 months following extracranial progression.

The analogous analysis of the full set of all patients including those with CNS disease present on initial staging reveals similar results: CNS failure was the first site of failure in 18 patients (23% of the 80 patients with CNS failure, 10% of the 175 patients that experienced *any CNS or non-CNS* failure), and detected synchronously with extracranial failure in three patients. In the remaining 59 patients with CNS failure (74% of the 80 patients with CNS failure, 34% of the 175 patients that experienced *any CNS or non-CNS* failure), extracranial failure preceded CNS failure, with a median time to CNS failure of 118 months following extracranial failure. In this set of all patients, 14 of the 18 patients presenting with CNS failure as first failure had CNS involvement on initial staging.

3.4 Survival

In the entire cohort of patients, median PFS and OS were 11.9 and 30.9 months, respectively (Figure 3). Median PFS was 12.0 and 11.9 months in the set of patients who presented initially with and without CNS involvement, respectively. On UVA, female gender, weight loss, increasing intrathoracic stage, initial CNS involvement, and greater number of extracranial metastases all correlated with worse OS (Table 3). On MVA, female gender, >5% weight loss, initial CNS involvement and 4 total extracranial metastases remained as independent predictors of worse OS.

4 Discussion

To our knowledge, this is the largest comprehensive analysis of prognostic factors and patterns of disease progression in metastatic EGFRmt NSCLC patients treated with erlotinib. Though smaller institutional retrospective reports of EGFRmt patients treated with erlotinib or gefitinib have suggested improved OS in those with exon 19 deletion versus exon 21 L858R mutation,^{21, 22} this is not confirmed in our dataset of initially-metastatic patients. Instead, we find worse OS in female patients and in those with initial CNS involvement, weight loss, or large extracranial metastatic burden (4 sites).

Furthermore, similar to the findings of Al-Halabi et. al., we find the predominant pattern of failure in our patients is within existing sites of disease, and that at two years, the cumulative incidence of such failure is over 50%, compared to a much smaller incidence of new- or combined-site failure.¹⁷ Younger age and lack of initial CNS involvement are both associated with ISF. Greater intrathoracic primary disease burden is associated with progression, and intrathoracic progression is *the sole site of initial failure* in nearly a third of patients that experience ISF. Rusthoven, et. al. from the University of Colorado performed a similar analysis on a smaller set of molecularly unselected patients at their institution and also found that the pattern of failure is frequently limited to initial sites of disease.¹⁶ Together, these data suggest a role for local therapy to known sites of disease as a means of prolonging time to progression, and potentially survival.

In contrast to previous studies, however, we have also performed a detailed analysis of CNS progression in patients without initial CNS involvement, which is of particular interest given that patients treated with erlotinib or gefitinib seem to have a prolonged time to new CNS failure.²³ Here, we find that the risk of CNS progression in those without initial CNS involvement is lower than the historical data for metastatic NSCLC and in accordance with previous reports, but hardly insignificant: the 2-year cumulative incidence of BM is 15%. By three years, this number goes up to 30% in our cohort. Why this risk is somewhat higher in our population than that previously reported by Heon, et. al. is unclear, but is comparable to that reported in a Korean series of metastatic NSCLC patients that responded to TKI.^{24, 25} Furthermore, in the majority of patients that experience CNS failure, it occurs relatively late and often *after* extracranial failure, thus likely from TKI-resistant clones that spread to the brain, especially given that most patients continue TKI therapy following initial progression. In addition, we find that patients with exon 21 L858R mutations have nearly twice the risk of BM as those with exon 19 deletions, also in contrast to earlier reports.

Ultimately, with respect to both CNS disease control as well as systemic control, the prolonged time to progression observed with TKIs in molecularly selected patients yields a prolonged period of stable disease control, but also more time for eventual escape by the tumor, most often via a T970M mutation in exon 20 or a new amplification of the *MET* oncogene in the case of NSCLC,^{26–28} and sometimes via small-cell transformation.^{20, 29} Given the largely concordant analyses showing local disease progression, and the growing body of data showing extended disease control via local therapy in relatively small series for oligoprogression of ALK+ NSCLC,¹³ or along with continued erlotinib for EGFRmt NSCLC with acquired resistance,¹⁵ or oligoprogression of either tumor type,¹⁴ there is an emerging rationale for an increased role of local therapy. Much of the reported data thus far has focused on local therapy delivered at the time of oligometastatic progression, with the logic that a few metastatic foci might be the only site where a clonal population that has escaped otherwise functioning molecular control for the balance of the patient's disease has taken hold. Local therapy to this oligometastasis might control this population while ongoing molecular therapy continues to control the remainder of disease elsewhere.

Here, we suggest another possibility. Based on our analysis showing that the site of first progression on erlotinib is usually limited to initially involved sites, it may be even more beneficial to incorporate local therapy upfront, at or near the time of TKI initiation, instead of waiting for maximal TKI response or for progression to occur. This would have the effect of reducing the initial pool of malignant clones, and therefore potentially increasing the time to a molecular event when a clone is likely to develop an escape pathway, at which point local therapy for oligoprogression may again offer continued disease control.

Our study and its inferences have several limitations which are inherent to retrospective analysis of this kind. Although these patients were all treated and followed at a single institution, variations in followup intervals and evaluations across individual patients and practitioners can limit the validity of adjudicating and dating the timing and pattern of failure. A minority of our patients also received systemic chemotherapy or local therapy prior to TKI, which could have unknown effects on subsequent tumor aggressiveness or control and thus pattern of progression. Furthermore, though it is not a direct focus of the current study, the effectiveness of salvage therapies on OS is not explored here.

5. Conclusions

Our data indicates that over half of patients with metastatic EGFRmt NSCLC treated with erlotinib are likely to fail at their initial sites of disease, and that younger age and lack of initial CNS involvement increase the likelihood of ISF. Furthermore, we indicate that patients without initial CNS disease are at significant risk to develop brain metastasis, and that EGFR exon 21 mutants are nearly twice as likely as exon 19 mutants to develop BM. The significant rates of CNS failure suggest that additional strategies to prevent CNS progression are needed, and could re-open the question of prophylactic cranial irradiation in this subset of NSCLC patients. This analysis provides further support for prospectively testing upfront local therapy in oligometastatic, molecularly selected NSCLC. A handful of such trials are now underway, including one at our institution and one in Hong Kong for

EGFRmt patients,^{30, 31} as well as one at the Massachusetts General Hospital that will include EGFR, ALK and ROS1 mutant patients.³²

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We analyzed failure patterns in EGFR-mutant NSCLC patients treated with erlotinib.
- Main pattern of progression was in initial sites of disease.
- Risk of developing brain metastasis was also substantial.
- This data supports earlier incorporation of local or brain-directed therapy.

Figure 1. Cumulative incidence of in-site failure (ISF), new-site failure (NSF), combined-site failure (CSF), or death without failure for the entire cohort of patients.

Figure 2.

A. Cumulative incidence of brain metastasis in the group of EGFRmt patients that presented initially without CNS involvement.

B. Cumulative incidence of brain metastasis segregated by EGFR exon 19 deletion or exon 21 L858R mutation.

Figure 3.
Overall survival for the entire cohort of EGFRmt patients treated with erlotinib.

Table 1

Baseline clinical characteristics of all patients and subset of initial CNS-free patients.

Characteristic	All patients (N=189) n (%)	Initial CNS-free Stage IV (N=111) n (%)
Age (continuous)	median 60 (range 26–89)	median 60 (range 29–88)
70	148 (78)	89 (80)
> 70	41 (22)	22 (20)
Gender		
M	56 (30)	33 (30)
F	133 (70)	78 (70)
KPS		
< 80	34 (18)	24 (22)
80	155 (82)	87 (78)
Weight loss		
0–5%	151 (80)	88 (79)
> 5%	38 (20)	23 (21)
History of Smoking		
No	127 (67)	76 (68)
Yes	62 (33)	35 (32)
Local stage		
I	14 (7)	13 (12)
II	17 (9)	10 (9)
IIIA	70 (37)	41 (37)
IIIB	88 (47)	47 (42)
EGFR mutation		
Exon 19 deletion	119 (63)	72 (65)
Exon 21 L858R	63 (33)	34 (31)
Other	7 (4)	5 (4)
Initial CNS involvement		
No	111 (59)	
Yes	78 (41)	
Total # extracranial metastases		
0	11 (6)	
1–3	46 (24)	34 (31)
4+	132 (70)	77 (69)
Total # extracranial metastatic sites		
0	11 (6)	
1	66 (35)	49 (44)
2+	112 (59)	63 (56)

Table 2

Predictors of failure limited to initial sites of disease (ISF)

UVA			
Factor	HR	95% CI	P-value
Younger age (continuous)	1.02	(1.00, 1.04)	0.014
Age (< 70 vs. ≥70)	2.01	(1.14, 3.54)	0.015
Gender (Female vs. Male)	0.75	(0.51, 1.12)	0.16
KPS (< 80 vs. ≥ 80)	1.52	(0.84, 2.7)	0.17
History of smoking (Yes vs. no)	0.75	(0.50, 1.13)	0.17
Weight loss (≥5% vs. 0–5%)	1.17	(0.73, 1.85)	0.52
Local stage (IIIA/IIIB vs. I/II)	1.55	(0.93, 2.58)	0.091
EGFR mutation (Exon 21 vs. Exon 19)	0.94	(0.63, 1.41)	0.76
EGFR mutation (Other vs. Exon 19)	0.40	(0.10, 1.60)	0.20
Initial CNS involvement (Yes vs. no)	0.73	(0.49, 1.08)	0.12
Total # extracranial mets (1+ vs. 0)	1.87	(0.71, 4.94)	0.21
Total # extracranial mets (4+ vs. 1–3, n=178)	1.01	(0.65, 1.56)	0.98
Total # extracranial met sites (2+ vs. 1, n=178)	0.84	(0.56, 1.25)	0.39
MVA			
Factor	HR	95% CI	P-value
Younger age (continuous)	1.02	(1.00, 1.03)	0.035
Gender (Female vs. Male)	0.73	(0.49, 1.09)	0.13
KPS (< 80 vs. ≥ 80)	1.55	(0.84, 2.84)	0.16
History of smoking (Yes vs. no)	0.78	(0.52, 1.17)	0.22
Local stage (IIIA/IIIB vs. I/II)	1.64	(0.99, 2.72)	0.056
Initial CNS involvement (No vs. yes)	1.60	(1.06, 2.43)	0.026

Table 3

Predictors of overall survival

UVA			
Factor	HR	95% CI	P-value
Younger age (continuous)	1.00	(0.99, 1.02)	0.88
Age (> 70 vs. ≤ 70)	1.41	(0.91, 2.20)	0.12
Gender (Female vs. Male)	1.68	(1.13, 2.51)	0.011
KPS (≤ 80 vs. > 80)	0.65	(0.42, 1.02)	0.060
Weight loss (> 5% vs. 0–5%)	1.72	(1.14, 2.58)	0.010
History of smoking (Yes vs. no)	0.79	(0.54, 1.15)	0.21
Local stage (IIIA/IIIB vs. I/II)	2.06	(1.23, 3.46)	0.006
EGFR mutation (Exon 21 vs. Exon 19)	0.94	(0.65, 1.37)	0.76
EGFR mutation (Other vs. Exon 19)	1.01	(0.37, 2.76)	0.99
Initial CNS involvement (Yes vs. no)	1.63	(1.15, 2.32)	0.007
Total # extracranial mets (1+ vs. 0)	1.16	(0.54, 2.49)	0.71
Total # extracranial mets (4+ vs. 1–3, n=178)	1.93	(1.25, 2.97)	0.003
Total # extracranial met sites (2+ vs. 1, n=178)	1.25	(0.87, 1.81)	0.23
MVA			
Factor	HR	95% CI	P-value
Younger age (continuous)	0.99	(0.98, 1.01)	0.45
Gender (Female vs. Male)	1.95	(1.27, 2.99)	0.002
KPS (≤ 80 vs. > 80)	0.74	(0.46, 1.20)	0.22
Weight loss (> 5% vs. 0–5%)	1.62	(1.04, 2.52)	0.034
Local stage (IIIA/IIIB vs. I/II)	1.39	(0.81, 2.40)	0.23
Initial CNS involvement (Yes vs. no)	1.65	(1.13, 2.41)	0.009
Total # extracranial mets (4+ vs. 1–3)	1.70	(1.09, 2.66)	0.019