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EGFR-tyrosine kinase inhibitor treatment beyond progression in long-term Caucasian responders to erlotinib in advanced non-small cell lung cancer: A case–control study of overall survival

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ABSTRACT

Introduction: Some patients with advanced NSCLC show prolonged disease stabilization on treatment with an EGFR-tyrosine kinase inhibitor (TKI) such as erlotinib. It is not clear how to treat patients who progress after prolonged response to erlotinib. We hypothesized that TKI therapy beyond progression with added chemotherapy, radiotherapy or best supportive care may improve survival.
Patients and methods: We retrospectively analyzed all NSCLC patients treated with erlotinib at our institutions since 2004who progressed after at least stable disease on erlotinib for at least 6 months. The first 16 patients did not receive further TKI treatment after progression (controls). The following 25 patients were treated with TKI beyond progression (TKI patients). Overall survival (OS) was analyzed for the whole population, a case–control analysis of pairs matched for gender, smoking status, and histology ($n = 28$), and for patients with known EGFR mutation status ($n = 23$).
Results: Treatment with TKI and chemotherapy was well tolerated. TKI-patients had a significantly longer OS from progression on TKI (case–control: median 14.5 vs. 2.0 months, HR 0.154) and longer OS from diagnosis of lung cancer (case–control: median 54.5 vs. 28.3 months, HR 0.474). An activating EGFR mutation was detected in 13 of the 23 patient tested (57%). Both among patients with and without detection of an activating EGFR mutation, those treated with erlotinib beyond progression had a longer survival.
Conclusions: In our case–control analysis in long-term erlotinib responders, treatment with TKI beyond progression in addition to chemotherapy or radiotherapy was feasible and lead to prolonged overall survival.

1. Introduction

The epidermal growth factor receptor (EGFR) has emerged as an important target in the treatment of NSCLC. Erlotinib and gefitinib are members of the "small molecule" tyrosine kinase inhibitors (TKI) of EGFR [1]. TKI-inhibitors have shown benefit as 2nd and 3rd line [2,3] and more recently in terms of PFS as 1st line therapy of EGFR mutation positive NSCLC [4–7]. Some patients with advanced NSCLC experience prolonged disease stabilization on treatment with erlotinib. After progression of such "long-term TKI responders", we and others [8] observed an unusually rapid disease progression, if TKI therapy was discontinued and replaced by conventional TKI-free therapy. In our data set of patients selected for TKI treatment according to clinical response criteria, patients with adenocarcinoma histology had a significantly prolonged PFS on erlotinib, but a shorter survival after progression and termination of TKI therapy than patients with non-adenocarcinoma histology [9]. Since adenocarcinoma histology and long-term response are clinical predictors of the presence of an activating mutation of the EGFR (EGFRM) [10,11], the rapid progression may be due to disinhibition

Abbreviations: AC, adenocarcinoma; BSC, best supportive care; CI, 95% confidence interval; EGFR, epidermal growth factor receptor; EGFRM, EGFR mutation; HR, hazard ratio; n.s., not significant; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumors; SD, stable disease; TKI, tyrosine kinase inhibitor; TKI-patients, patients treated with TKI beyond progression.

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Table 1
Baseline data (at progression on TKI) and treatment after progression.

	Whole population		Case–control patients	
	Patients treated with TKI beyond progression	Controls	Patients treated with TKI beyond progression	Controls
n	25	16	14	14
Age (mean, range)	64.4 (44–83)	67.4 (45–84)	65.8 (44–83)	67.7 (45–84)
Stage				
UICC IIIB	5 (20%)	4 (25%)	3 (21.4%)	3 (21.4%)
UICC IV	20 (80%)	12 (75%)	11 (78.6%)	11 (78.6%)
Performance status (ECOG)				
ECOG 0	7 (28%)	4 (25%)	4 (28.6%)	4 (28.6%)
ECOG 1	15 (60%)	10 (62.5%)	8 (57.1%)	8 (57.1%)
ECOG 2	3 (12%)	2 (12.5%)	2 (14.3%)	2 (14.3%)
Gender				
Male	9 (36%)	9 (56.3%)	8 (57.1%)	8 (57.1%)
Female	16 (64%)	7 (43.8%)	6 (42.9%)	6 (42.9%)
Smoking status				
Current smokers	0	0	0	0
Former smokers	6 (24%)	8 (50%)	6 (42.9%)	6 (42.9%)
Never smokers	19 (76%)	8 (50%)	8 (57.1%)	8 (57.1%)
Histology				
Adenocarcinoma	23 (88.9%)	13 (81.3%)	13 (92.9%)	13 (92.9%)
Large cell carcinoma	1 (3.7%)	1 (6.3%)	0	0
Squamous cell carcinoma	1 (7.4%)	2 (12.5%)	1 (7.1%)	1 (7.1%)
EGFR mutation				
Tested	15	8	11	5
Positive exon 19	8	3	4	1
Positive exon 21	0	1	0	1
Positive exon 18	1	0	1	0
Negative	6	4	6	3
Unknown	10	8	3	9
Therapy line (erlotinib)				
1st line	5 (20%)	4 (25%)	4 (28.6%)	4 (28.6%)
2nd line	19 (56%)	11 (68.8%)	10 (71.4%)	10 (71.4%)
≥3rd line	1 (4%)	1 (6.3%)	0	0
Best response to erlotinib				
Complete remission	1 (4%)	1 (6.3%)	1 (7.1%)	1 (7.1%)
Partial remission	19 (56%)	9 (56.3%)	10 (71.4%)	9 (64.3%)
Stable disease	5 (20%)	6 (37.5%)	3 (21.4%)	4 (21.6%)
PFS from start of TKI therapy (median, months)	15.5	12.0	12.5	12.0
Treatment after progression				
Chemotherapy	17 (68%)	9 (56.3%)	11 (78.6%)	9 (64.3%)
Radiotherapy	7 (28%)	4 (25%)	4 (28.6%)	3 (21.4%)
BSC only	6 (24%)	6 (37.5%)	4 (28.6%)	5 (35.7%)

Controls are patients not treated with TKI beyond progression. The case–control subpopulation was matched individually for gender, smoking status, histology, best response to first TKI therapy, and therapy line (14 pairs). After progression on TKI, patients were treated with chemotherapy and radiotherapy, or best supportive care (BSC). TKI patients continued to receive erlotinib. Control patients received TKI-free therapy. Some patients received more than one line of chemotherapy or both chemotherapy and radiotherapy after progression resulting in sums > 100%. In two TKI patients, cerebral metastasis (one recurrence, one new metastasis) were resected under erlotinib with no surgical complications. The new metastasis occurred in a patient with an activating mutation in exon 19 of the EGFR gene which was also detected in the resected metastasis. The metastasis did not carry the common TKI resistance mutation T790M.

of the intrinsically activated EGFR and rapid EGFR-driven tumor growth. This is supported by a PET-CT study showing a reversible increase in tumor growth and glucose uptake after termination of EGFR-TKI treatment [12].

Lung cancer shows a significant intra-tumor genetic heterogeneity. For example, in 30% of EGFRM-positive resected lung cancer, both EGFR-negative and EGFRM-positive cancer cells have been demonstrated [13]. Thus, TKI resistance by an acquired second mutation e.g. T790M may occur in (the progressive) part of the tumor, whereas other manifestations of the tumor may still be sensitive to TKI therapy [14]. Therefore, the oncological paradigm to discontinue a line of therapy upon progression which was derived from classical chemotherapy may not be valid for molecularly targeted therapies such as EGFR-TKI. It might therefore be reasonable to continue TKI therapy beyond progression and add chemotherapy, radiotherapy, local surgery or BSC as appropriate rather than to discontinue TKI and use standard therapy alone. A similar approach has been used successfully with trastuzumab and lapatinib in HER2-positive breast cancer with significant improvement in PFS [15–17].

2. Patients and methods

We retrospectively analyzed all NSCLC patients treated with erlotinib (standard dose 150 mg p.o. once daily) at our institutions (two teaching hospitals and a regional oncology outpatient clinic) since 2004 who progressed after disease stabilization (complete or partial remission or stable disease) on erlotinib for at least 6 months. These patients had generally been selected using the clinical response criteria adenocarcinoma, female gender, and never smoking status [8], since routine testing for EGFR mutation status became available in Germany only in July 2010. For