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Retreatment with erlotinib: Regain of TKI sensitivity following a drug holiday for patients with NSCLC who initially responded to EGFR-TKI treatment

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ABSTRACT

Background: Tyrosine kinase inhibitors (TKI) of the epidermal growth factor receptor (EGFR) are approved as treatment of non-small-cell lung cancer (NSCLC). Despite an initially impressive response to EGFR-TKIs, patients with an activating EGFR mutation invariably relapse. For these patients few treatment options are available after additional progression during or after chemotherapy. The aim of this study is to examine the effect of retreatment with an EGFR-TKI after a drug holiday.

Patients and methods: We retrospectively reviewed the medical records of 14 patients with stage IV NSCLC who progressed after long-term disease control with EGFR-TKI, who were subsequently treated with standard chemotherapy and at renewed progression retreated with EGFR-TKI.

Results: Fourteen patients (five male, nine female, median age 55 years (39–70 years) received retreatment with erlotinib. The median interval from the discontinuation of EGFR-TKI to the 2nd episode was 9.5 months (3–36 months). Before starting retreatment 36% ($n = 5$) had a T790M mutation. Retreatment resulted in 36% ($n = 5$) partial response, 50% stable disease ($n = 7$) and 14% progressive disease ($n = 2$). Among patients with a T790M mutation this number was two, one and two, respectively. Seven patients are still on therapy without signs of progression. Median follow up is 9 months (1.5–16+ months) and median PFS is 6.5 months (1–16+ months).

Conclusion: Our findings suggest that retreatment with erlotinib is an option for patients with NSCLC who initially benefited from previous EGFR-TKI treatment and progressed after standard cytotoxic chemotherapy.

1. Introduction

Tyrosine kinase inhibitors (TKIs) of the epidermal growth factor receptor (EGFR) are globally approved as treatment in any line of non-small-cell lung cancer (NSCLC).[1,2] For gefitinib, the overall objective response rate in treatment-naïve patients in a population where the incidence of activating EGFR mutations is over 60% has recently been reported in two Asian studies to be higher than 70%.[3,4]

Patients with an activating EGFR mutation who initially respond to EGFR-TKI invariably relapse with resistant disease. The median time to progressive disease was recently reported

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in an American population to be 12 months.[5] The molecular mechanism of resistance to therapy is poorly understood. Possible explanations are EGFR T790M mutations (in exon 20), amplification of the met proto-oncogene (MET) or activation of other receptor tyrosine kinases.[6] If feasible, the next treatment step is conventional chemotherapy. Maemondo et al. reported a response rate of 28.8% for carboplatin–paclitaxel as second-line treatment after gefitinib.[4]

Nonetheless, the majority of this patient group will eventually develop progressive disease after cytotoxic treatment. Apart from further chemotherapy, the clinical management of these patients has not been defined. Interestingly, a regained drug sensitivity for TKIs was recently found in PC9 NSCLC cell lines.[7] A non-mutational, reversible, EGFR-TKI drug resistance mechanism was suggested, which was overcome by a 'drug holiday'. In addition, two case reports showed a retreatment response in men.[8,9]

The aim of this retrospective study was to examine whether retreatment with an EGFR-TKI after a drug holiday might be of benefit.

2. Patients and methods

We retrospectively reviewed the records of patients in our institution who were treated with an EGFR-TKI for two separate periods. Inclusion criteria were NSCLC stage IV with an initial response to TKIs according to the RECIST criteria.[10] Activating mutations in the EGFR gene were assessed in tumour biopsies by high resolution melting curve analysis followed by sequencing.[11] At disease progression the TKI was discontinued and patients received conventional platinum based chemotherapy. At renewed progression, patients were retreated with an EGFR-TKI. Before TKI retreatment new tumour biopsy specimen were obtained for mutational analysis in 12 patients. cMet amplification was not assessed.

We assessed the RECIST-defined response rate of the reintroduction of a TKI and the progression free survival.

3. Results

Fourteen patients fulfilled the inclusion criteria (Table 1). Before starting the initial treatment with an EGFR-TKI, 11 patients had an exon 19 deletion, one patient an exon 21 point mutation (L858R), and in two patients (who fulfilled the Jackson criteria) no mutational analysis was performed.[12] Sixty-four percent of the patients were female and the median age was 55 years. All except one patient were treated with erlotinib. In one patient this was combined with sorafenib. All patients showed progression after previously achieved long term (median 12.5 months, range 7–34) disease control on treatment with EGFR-TKI. In 12 patients new tumour biopsies were obtained. Mutation analyses revealed an additional T790M mutation in EGFR exon 20 in five patients with an exon 19 deletion. In six patients an exon 19 deletion was confirmed and one patient had an exon 21 point mutation (L858R).

In all cases the EGFR-TKI after the 'drug holiday' was erlotinib. In three patients this was in combination with cetuximab. The median interval between the first and second episode of EGFR-TKI treatment was 9.5 (3–36) months in which patients received conventional chemotherapy. In 13 patients this consisted of a platinum-based doublet. Ninety-three percent had either PR ($n = 7$) or SD ($n = 6$) to chemotherapy. Progression free survival following treatment with cytotoxic chemotherapy was 4 (1–13) months. With erlotinib retreatment starting at progression, 86% of the patients had either PR ($n = 5$) or SD ($n = 7$), PD was seen in two (Table 2). Among patients with a T790M mutation two patients had PR, one SD and two PD. Two out of three patients who also received cetuximab on retreatment had PD and one PR. Seven (50%) patients are still on treatment, of whom one for more than 16 months now. The medium follow up is 9 (1.5–16+) months. The median progression free survival is 6.5 (1–16+) months. Side-effects, especially skin rash were common (Table 2).

On starting retreatment two patients received an erlotinib dose that was 50 mg higher than in the first treatment period. One patient had PR and one SD. Two other patients had a dose which was 50 mg lower than in the first period due to toxicity. One of them had PR and one SD.

4. Discussion

The salient point of this retrospective study is that a drug holiday may regain drug 'sensitivity' to TKIs. Fourteen patients with NSCLC, who had PD after an initial response to a TKI were treated with chemotherapy. After progression on chemotherapy, 86% of the patients again responded to treatment with erlotinib. In addition, a PFS of more than 6 months is noteworthy in third line therapy. Retreatment response has already been described for conventional chemotherapy, but, to the best of our knowledge, not for series of patients treated with erlotinib.[13]

Acquired resistance to TKIs is common among patients with EGFR- mutant lung cancer. After a median time of 12 months patients invariably relapse.[5] EGFR T790M mutation is the most common finding in tumour biopsies from patients with acquired resistance.[14] A recent study showed an indolent clinical course of patients with this mutation with a median survival after PD of 16 months.[5] We biopsied 12 out of 14 patients after PD of whom 5 (42%) showed T790M. Interestingly, three of them nevertheless had a retreatment response. Therefore, other factors have to play a role as well. A selection process due to chemotherapy or to the lack of EGFR-TKI may lead to a reduction of the fraction of tumour cells with an additional T790M compared to those solely exhibiting the activating EGFR mutation. Thus, the balance of single activating mutations and activating mutations plus T790M mutations will dictate the probability of a measurable response to EGFR-TKIs. Also, this finding has implications for design of clinical trials aimed at so called EGFR-TKI resistant patients.

Furthermore, non-mutational changes may be an explanation of this dynamic reversibility of resistance. Sharma et al. found that in a human lung-cancer cell line (PC9) that was treated with erlotinib, most cells quickly died, but a small number persisted.[7] These drug-tolerant persisters remained spontaneously from single drug-sensitive clones. Continued

Table 1 – Patient characteristics.

	Median (range)
Age (years)	55 (39–70)
Response duration to 1st time TKI (months)	12.5 (7–34)
	Number (%) of patients
Male/female	5 (36)/ 9 (64)
EGFR status prior to first TKI treatment	
Deletion exon 19	11 (79)
Point mutation 21	1 (7)
Unknown	2 (14)
EGFR status prior to second TKI treatment	
Deletion exon 19	6 (43)
Deletion exon 19 + T790M	5 (36)
Point mutation 21	1 (7)
Point mutation 21 + T790M	0
Unknown	2 (14)
Chemotherapy	
Platinum-based doublet	13 (93)
Pemetrexed	1 (7)
Initial response to chemotherapy	
Partial remission	7 (36)
Stable disease	6 (43)
Progressive disease	1 (7)
Initial TKI → second TKI	
Erlotinib → erlotinib	8 (57)
Erlotinib → erlotinib + cetuximab	2 (14)
Erlotinib + sorafenib → erlotinib	3 (21)
Gefitinib → erlotinib + cetuximab	1 (7)

EGFR, epidermal growth factor receptor, TKI, tyrosine kinase inhibitor.

Table 2 – Results of TKI retreatment.

	Median (range)
Length of TKI 'holiday' (months)	9.5 (3–36)
Follow-up after retreatment (months)	9 (1.5–16+)
Progression free survival (months)	6.5 (1–16+)
	Number (%) of patients
Response to reintroduction of TKI	
Partial remission	5 (36)
Stable disease	7 (50)
Progressive disease	2 (14)
Toxicity	
Skin rash grade 1–3	6 (43)
Hair loss grade 2	1 (7)
Diarrhoea grade 1	3 (21)
Esophagitis grade 1	1 (7)
Paronychia	1 (7)
Dose reduction	3 (21)

culture of these cells in drug-free media gave rise to drug-sensitive cells (in 9–90 doublings). The authors concluded that altered regulation of chromatin might be the underlying mechanism for this phenomenon. Besides, increased IGF1R activity was also detected in the drug-tolerant cells. Targeting this receptor may be an interesting strategy for prevention of non-mutational resistance.

The percentage of patients that exhibited an objective response to conventional chemotherapy after PD on TKI was large (93%). Maemondo et al. report in a subgroup analysis among patients who were treated with gefitinib as first line regimen, a response rate to carboplatin–paclitaxel of only 28.8%.[4] A possible explanation of this difference may be population difference (Japanese versus Caucasian). Another difference is the chemotherapy scheme; we merely used cisplatinum-pemetrexed instead of carboplatin–paclitaxel. Finally, our patients were treated with erlotinib instead of gefitinib (except for one).

A limitation of this study may be the retrospective design with its inherent shortcomings. Another limitation may be that not all patients received the same erlotinib dose. However, only two patients received a higher erlotinib dose compared to the first treatment period. Since two patients who received a lower dose also responded to the erlotinib retreatment, it is unlikely that the erlotinib dose has influenced the results. A third limitation may be that in three patients retreatment with erlotinib was combined with cetuximab. Two of them had PD and one PR. In fact, they were the only patients with PD. Therefore, the effect of the erlotinib retreatment cannot be explained by cetuximab. A recently published phase II trial on this combined treatment after acquired resistance to erlotinib indeed failed to demonstrate significant activity.[15]

In conclusion, retreatment with erlotinib is an option for patients with NSCLC who initially benefitted from previous EGFR-TKI treatment and recurred after standard cytotoxic chemotherapy. In addition, T790M mutation in EGFR exon 20 does not exclude response to TKI retreatment.

Conflict of interest statement

Dr. F.B. Thunnissen: advisory board fee from ASTRA Zeneca, Professor P.E. Postmus: advisory board and speakers fee from Roche, department of pulmonology: research grant from Roche. The remaining authors have no conflicts of interest.

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