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RESEARCH

Disease Flare After EGFR Tyrosine Kinase Inhibitor Cessation Predicts Poor Survival in Patients with Non-small Cell Lung Cancer

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Abstract Available study revealed non-small cell lung cancer (NSCLC) patients faced a risk of disease flare after cessation of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) treatment. There was no data concerning the prognostic value of disease flare. This study aimed to investigate the prevalence of disease flare in a Chinese cohort, and analyzed its prediction to survival. A cohort of 227 NSCLC patients with acquired resistance to EGFR TKI was retrospectively analyzed. Prevalence and clinical features of disease flare after TKI cessation were reviewed. Survival data were analyzed between patients with flare and those without flare. EGFR gene mutations in tumors were detected. Twenty of 227 (8.8 %) patients were determined with disease flare after TKI cessation. The median interval from TKI cessation to disease flare was 7 days (range 3–18). Forty percent of patients complained of deteriorated dyspnea attributable to malignant effusion. Thirty percent of patients had progressive lesions in the brain. After TKI cessation 35 % of flare patients died before challenge of subsequent treatment. No response was observed in 30 % of flare patients undergoing subsequent chemotherapy. When compared with the non-flare group, patients with disease flare demonstrated comparable progression-free survival (10.1 vs. 9.9 months; P=0.973), shorter post-TKI survival (4.1 vs. 6.1 months; P<0.001), and a significantly poor overall survival (16.6 vs. 21.6 months; P=0.002). Disease flare after cessation of EGFR TKI occurred in Chinese NSCLC population and predicted a poor survival.

Keywords Non-small cell lung cancer · Epidermal growth factor receptor · Tyrosine kinase inhibitor · Cessation · Disease flare

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Introduction

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) gefitinib or erlotinib was effective in non-small cell lung cancer (NSCLC) with EGFR activating mutations [1–4]. However, acquired resistance was developed inevitably after about 12-month disease control. The molecular mechanism of acquired resistance was not fully elucidated, although a few candidates including the secondary EGFR T790M mutation or c-MET gene amplification were detected [5–7]. There was no standard biomarker-guided treatment on acquired resistance to TKI. After radiological progressive disease (PD), sporadic reports showed continuation of EGFR TKI could still produce clinical benefit in a specific subset of patients, but stopping EGFR TKI and switch to chemotherapy beyond progression was generally applied in clinical practice [8, 9]. However, EGFR TKI cessation may induce a risk of disease rapid exacerbation within a short time, which was defined as a phenomenon of disease flare [10, 11]. A study in Caucasian population showed the rate of disease flare achieved 23 % (14/61) after stopping EGFR TKI [10]. Molecular mechanisms for disease flare were still unclear. Due to the difference of genetic background between the Caucasian and Asian population, further investigation into disease flare in Asian patients is indispensable and clinically significant. Furthermore, there was no data about the impact of disease flare on patient survival. This may remain as an obstacle in patient subsequent management after EGFR TKI failure.

We hypothesize NSCLC patients with disease flare occurrence after EGFR TKI cessation could have a shorter survival. A cohort of Chinese patients with acquired resistance to EGFR TKI was retrospectively analyzed to investigate the prevalence and prognostic value of disease flare.

Materials and Methods

Patients

A total of 700 patients with pathologically confirmed locally advanced or metastatic NSCLC, who underwent EGFR TKI (gefitinib or erlotinib) therapy were reviewed from June, 2002 to August, 2011 at Guangdong General Hospital (GGH) [12, 13]. Two-hundred and twenty seven patients achieved a ≥3-month disease control on initial EGFR TKI treatment and finally became resistant to TKI were accrued into the analysis [14]. Clinical trial participants occupied 52.9 % (120/227) of the population, and the rest 47.1 % (107/227) were non-trial patients. Their corresponding clinical information was from the electronic medical record database of Guangdong Lung Cancer Institute (GLCI). The radiographic response to EGFR TKI treatment was determined according to RECIST (Response Evaluation Criteria in Solid Tumors) [15]. Tumor specimens were retrieved from the GLCI tumor tissue bank. The study was approved by the institutional review boards of GGH. All patients provided informed consent. The last follow up was February 27th, 2012.

Study Design

Disease flare was defined as hospitalization or death attributable to tumor progression after stopping the TKI and before initiation of subsequent therapy; the washout interval was ≤21 days [10]. Clinical and molecular characteristics of patients with disease flare were reviewed. Survival data including progression-free survival, post-TKI survival and overall survival were compared between the non-flare group and disease flare group.

EGFR Gene Mutation

Mutations in exons 18–21 of the tyrosine kinase domain of the EGFR gene in patients with disease flare were tested in EGFR-TKI-naïve or TKI-resistant tumors using a polymerase chain reaction (PCR)-based direct sequencing method [16, 17].

Statistical Analysis

Chi-square or continuity correction tests were used to compare qualitative data. Progression-free survival (PFS) was defined as the time from commencement of EGFR TKI treatment to the documentation of disease progression or death from any cause. Post-TKI survival was calculated from EGFR TKI cessation to the last visit or death from any cause. Overall survival (OS) was calculated from commencement of EGFR TKI treatment to the last visit or death from any cause. Survival curves among patient groups were compared by the Log-rank test. All statistical tests were two-sided and $P<0.05$ was considered to be statistically significant.

Results

Prevalence of Disease Flare

Twenty of 227 (8.8 %) patients were defined as disease flare after EGFR TKI cessation (Fig. 1). Gender, age, EGFR mutational status, line of TKI treatment, best response to TKI, and length of TKI administration were not correlated with the prevalence of disease flare (Table 1).

Characteristics of Patients with Disease Flare

Of the 20 patients with disease flare, 70 % (14/20) were female, 80 % (16/20) were non-smoker, 75 % (15/20) were with PS=1, 90 % (18/20) were with adenocarcinoma and absence of brain metastasis at the baseline; 45 % (9/20) of them underwent EGFR TKI in the first line setting (Table 1). Six patients (30 %) received chemotherapy as subsequent treatment, and no response was observed (3*SD and 3*PD); Seven patients (35 %) died before challenge of subsequent treatment.

The median washout interval before disease flare was 7 days (range 3–18). Of these patients, 40 % (8/20) complained of deteriorated dyspnea attributable to progressive disease in pleura (6 patients) or pericardia (2 patients); six

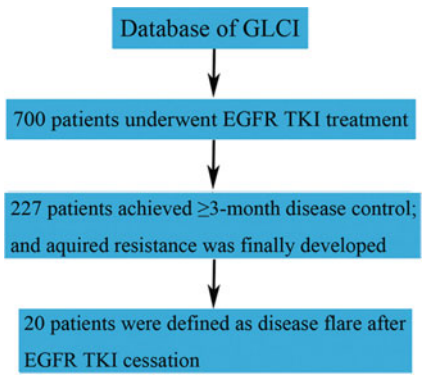

Fig. 1 Flow chart of screening patients with disease flare. GLCI, Guangdong Lung Cancer Institute

Table 1 Patient characteristics and prevalence of disease flare

Factor	Non-flare	Flare	*P* value
Gender			
Male	90	6	0.244
Female	117	14	
Age(year)			
≤60	115	11	0.962
>60	92	9	
EGFR status[a]			
Activating mutation	150	14	0.372[b]
Wild type	20	4	
Line of TKI			
1st	103	9	0.684
≥2st	104	11	
Best response to TKI			
RR	166	12	0.070
SD	41	8	
Length of TKI treatment (month)			
≤12	107	10	0.885
>12	100	10	
Total	207	20	

[a] Thirty-nine patients with unknown EGFR were excluded

[b] Continuity correction test. TKI, tyrosine kinase inhibitor

patients (30 %) were found to have progressive lesions in the brain (Table 2).

EGFR Mutations in Patients with Flare

In pre-TKI tumors, 5 cases were detected with EGFR exon 19 deletion; 8 cases with exon 21 point mutation; 1 case had exon 18 plus 21 double mutation; 4 cases were wild type; and EGFR was unknown in 2 cases. In TKI-resistant tumors, 3 cases were found with exon 19 deletion; 2 cases with exon 21 point mutation; 5 cases were wild type; and EGFR was unknown in 10 cases. For 9 patients with paired specimens, 2 patients with activating mutation in pre-TKI tissues were detected as wild type on post-TKI tumors.

Survival Analysis

No significant differences were found between the non-flare group and disease flare group regarding the PFS (10.1 vs. 9.9 months, P=0.973; Fig. 2). When compared with the non-flare group, patients with disease flare demonstrated a significantly shorter post-TKI survival (4.1 vs. 6.1 months, P<0.001; Fig. 3), and a poorer OS (16.6 vs. 21.6 months, P =0.002; Fig. 4).

Discussion

Our data firstly reported the prevalence of disease flare after EGFR TKI cessation in an Asian NSCLC population. The

Table 2 Progression overview in patients with disease flare

No.	Symptomatic deterioration	Progressive sites	Events	Interval[a] (day)
1	Dyspnea	Pleural effusion	Hospitalization	13
2	Dyspnea	Pleural effusion, lungs, and supraclavicular LN	Death	7
3	Emotional unresponsiveness	lungs and brain	Death	18
4	Dyspnea	Pleural effusion	Hospitalization	3
5	Dyspnea	Pericardial effusion and liver	Hospitalization	7
6	Cough	Liver	Hospitalization	7
7	Dyspnea	Pericardial effusion	Hospitalization	5
8	Dyspnea	Pleural effusion	Hospitalization	12
9	Deteriorated PS	Liver, lung, and chest wall	Hospitalization	13
10	Deteriorated PS	Multiple brain	Death	8
11	Headache	Multiple brain	Death	18
12	Dyspnea	Pleural effusion	Hospitalization	4
13	Dyspnea	Pleural effusion	Hospitalization	18
14	Dyspnea	Lung and mediastinal LN	Death	4
15	Hemoptysis	Lungs	Death	4
16	Headache	Multiple brain	Hospitalization	12
17	Coma	Multiple brain	Death	5
18	Bone pain	Multiple bones	Hospitalization	7
19	Bone pain	Multiple bones	Hospitalization	5
20	Seizure	Multiple brain	Hospitalization	8

[a] Time from TKI cessation to the onset of disease flare. *LN* lymph nodes; *PS* performance status

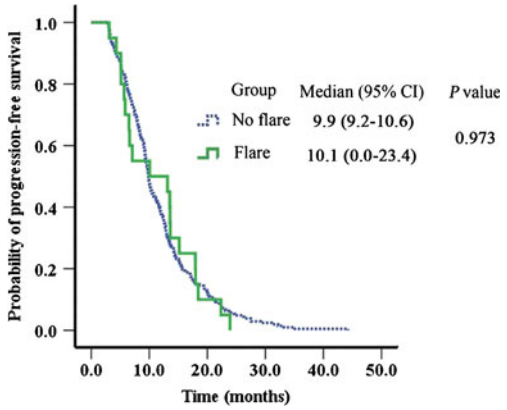

Fig. 2 Progression-free survival

rate of disease flare (8.8 %) seemed lower than that in the Caucasian patients (23.0 %). As the time to disease flare in Caucasian patients varied from 3 to 21 days, our analysis defined the occurrence of disease flare according the available literature, and set the upper limit of EGFR TKI washout period as 21 days [10]. Another support came from findings of PET/CT scans: three weeks after stopping erlotinib or gefitinib, there was a median 18 % increase in SUV_{max} and 9 % increase in tumor diameter [18]. Theoretically hospitalization or death due to tumor progression was classified as disease flare, but a proportion of patients with poor PS would not undergo radiologic assessments after TKI cessation, when best supportive care (BSC) was proposed and anti-cancer therapy would be intolerable. Thus, occasionally accurate determination of disease flare in clinical practice was challenging due to its general description and incorporated subjectivity. More evidence about tumor biology would help the clinicians in defining disease flare.

In the Chinese NSCLC patients with disease flare, 40 % of the group demonstrated exacerbated dyspnea and progressive malignant effusion; 30 % of them had brain involvement. Tumor metastatic affinity to pleura or brain in this setting was not elucidated. Our finding was in accordance with the available data [10]. Progressive malignant effusion could predict a poor prognosis, and the new lung cancer staging system reclassified tumor induced effusion as M_{1a} instead of T_4 [13]. In the analysis of 127 Korean NSCLC patients with clinical benefit to EGFR TKI, the first site of failure was central nervous system (CNS) involvement in 33 (26 %) patients [14]. Omuro et al. reported that the incidence of the CNS as an initial failure site reached 33 % in EGFR TKI responders with advanced NSCLC [19]. For patients with acquired resistance to EGFR TKI, brain lesions could flare in subsets when the exposure of TKI was withdrew. As brain metastasis had negative effects on quality of life and overall survival in NSCLC patients, management of brain lesions should be a concern when the EGFR TKI treatment was stopped [20, 21].

The available data revealed EGFR mutant cells with resistance to gefitinib can become sensitive once again in the absence of the TKI [22]. Clinical observations found after a period of TKI washout patients can respond again to re-administration of EGFR TKI, and suggested TKI-withdrawal, switch to chemotherapy and then re-challenge of TKI after a "drug holiday" as a strategy to counter acquired resistance [23, 24]. But the occurrence of disease flare made a subset of NSCLC patients face a risk of accelerated disease exacerbation on TKI cessation. Thirty percent of patients with disease flare in our study received chemotherapy as subsequent treatment, and no response was observed; thirty-five percent of flare patients died before the challenge of subsequent treatment. Randomized phase III trials showed EGFR TKI and platinum-based doublet chemotherapy in the first-line setting produced similar OS [25, 26]. One of the explanations was the imbalanced crossover treatments in the second-line setting; patients underwent first-line EGFR TKI had a relatively lower percentage of subsequent chemotherapy. Disease flare after TKI cessation occurred in a small proportion of patients may result in less chance of subsequent chemotherapy. To the best of our knowledge, our study firstly reported patients with disease flare demonstrated a significant shorter post-TKI survival and poorer OS. Our findings showed the negative impact of disease flare on prognosis,

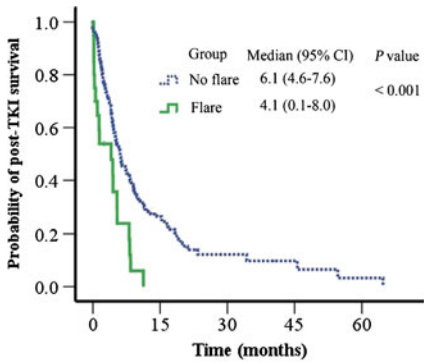

Fig. 3 Post-TKI survival. TKI, tyrosine kinase inhibitor

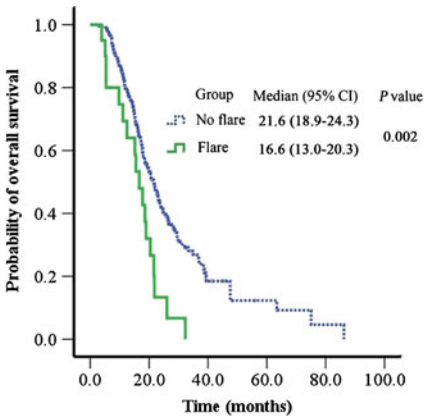

Fig. 4 Overall survival

which could explain in part that relatively long PFS on first-line EGFR TKI arm was not translated into prolonged OS in the abovementioned clinical trials.

This study had intrinsic limitations. As a retrospective design, risk factors for disease flare could not be established in the analysis. Second, molecular mechanism about disease flare after EGFR TKI cessation remained elusive. We analyzed EGFR mutations in patients with disease flare: 90 % (18/20) of pre-TKI tumors and 50 % (10/20) of post-TKI tumors. We failed to clarify the relationship between occurrence of disease flare and molecular variations. No secondary EGFR T790M mutation was detected; the results showed EGFR T790M did not correlate with the prevalence of disease flare, which was in agreement with the available report [10].

In summary, disease flare after cessation of EGFR TKI occurred in Chinese NSCLC population and predicted a poor survival. Prospective data and further investigations into underlying molecular mechanisms are warranted.

Conflict of Interest Statement The author(s) indicated no potential conflicts of interest.

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