Lung Cancer 79 (2013) 33–39

Contents lists available at SciVerse ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Clinical modes of EGFR tyrosine kinase inhibitor failure and subsequent management in advanced non-small cell lung cancer

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ARTICLE INFO

Article history:
Received 3 July 2012
Received in revised form 30 August 2012
Accepted 24 September 2012

Keywords:
Non-small-cell lung cancer
Epidermal growth factor receptor
Tyrosine kinase inhibitor
Failure
Mode

ABSTRACT

Background: There is no published overview of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) failure modes in advanced non-small-cell lung cancer (NSCLC). This study aimed to classify the diversity of EGFR-TKI failure, and to investigate the usefulness of clinical modes in subsequent management and prognosis.

Methods: One-hundred and twenty consecutive clinical trial patients with EGFR-TKI failure were enrolled as the training set to establish a clinical model based on clinical factors. Another 107 routine patients were enrolled as the validating set according to a Bayes discriminant analysis. EGFR mutations and c-MET amplification were analyzed. Kaplan–Meier survival analysis was used to test the differences among three clinical modes and subsequent management.

Results: The duration of disease control, evolution of tumor burden, and clinical symptom were verified as feasible grouping variables. A correct grouping rate achieved 87.9%. The cohort was classified into three groups, as follows: 130 patients with dramatic progression, 42 with gradual progression, and 55 with local progression. Progression-free survivals (PFSs) for the dramatic progression, gradual progression, and local progression groups were 9.3, 12.9, and 9.2 months, respectively ($P = 0.007$). Overall survivals for the groups (OSs) were 17.1, 39.4, and 23.1 months, respectively ($P < 0.001$). TKI continuation was superior to switching chemotherapy in a subsequent setting for gradual progression (39.4 months *vs.* 17.8 months; $P = 0.02$). The difference of EGFR or c-MET among the three groups was not significant.

Conclusions: Clinical modes of EGFR-TKI failure could favor strategies for subsequent treatment and predicting a survival benefit in advanced NSCLC.

1. Introduction

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) gefitinib and erlotinib have shown efficacy in the treatment of advanced non-small cell lung cancer (NSCLC) with EGFR mutation [1]. Six randomized trials have demonstrated a significantly higher tumor response rate and longer progression-free survival (PFS) in EGFR-mutant patients treated with first-line TKI [2–7]; however, most developed gefitinib or erlotinib failure. On treatment failure, many patients had a secondary EGFR T790M mutation, c-MET amplification, or both [8–11]. A clear definition of acquired resistance has been described to help create standard entry criteria for clinical trials of such patients, regardless of molecular biomarkers of acquired resistance to EGFR-TKI [12]. The diversity of TKI failure has been reported sporadically, including rapid deterioration of clinical symptoms or frequent central nervous system involvement [13,14]. However, there is no published overview of EGFR-TKI failure modes.

Treatment subsequent to EGFR-TKI failure is challenging. No genotype-directed standard therapy exists for patients with gefitinib or erlotinib failure; cytotoxic therapies are generally used [15]. In patients with EGFR-TKI failure, the median OS and PFS from the time of TKI resistance in the subsequent chemotherapy group (11.2 and 3.5 months, respectively) were significantly longer than those in the best supportive care (BSC) group (3.8 and 1.5 months, respectively; $P < 0.01$) [16]. Some patients may still benefit from EGFR-TKI after acquired resistance. Re-administration of TKI in two cohorts of previously TKI-responsive NSCLC patients upon radiographic progression decreased the rate of clinical deterioration and stabilized some of the lesions [17,18]. Currently, it is unclear whether continued use of gefitinib or erlotinib is superior to subsequent switching to chemotherapy for patients with failure to either drug in

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http://dx.doi.org/10.1016/j.lungcan.2012.09.016

clinical practice. We hypothesize the diversity of EGFR-TKI failure can be categorized into distinct modes according to clinical circumstances; these modes should be managed accordingly. Thus, we evaluated retrospectively the feasibility of defining various modes of EGFR-TKI failure and investigated the correlation with survival benefit or genetic variation.

2. Materials and methods

2.1. Study population

Two-hundred and twenty-seven patients with pathologically confirmed locally advanced or metastatic NSCLC were enrolled into the study from June 2002 to August 2011 at Guangdong General Hospital (GGH). The last follow up was February 27th, 2012. One-hundred and twenty patients were from the TRUST, IPASS, OPTIMAL, and CTONG0901 (NCT01024413) trials [2,6,19]. The remaining 107 patients received treatment in routine practice. Tumors were subtyped histologically according to the World Health Organization (WHO) classification [20]. The radiographic response to EGFR-TKI treatment was determined according to RECIST (Response Evaluation Criteria in Solid Tumors) [21]. All patients achieved a ≥3-month disease control after EGFR-TKI treatment [14]. The objective tumor response was evaluated every 6–8 weeks. Additional assessments were performed based on clinical circumstances. Clinical data were from the electronic medical record database of Guangdong Lung Cancer Institute (GLCI). Tumor specimens were retrieved from GLCI tumor tissue bank. The study was approved by the institutional review boards of Guangdong General Hospital (GGH). Informed consent was obtained from each patient.

2.2. Study design

Based on Jackman's clinical definition of acquired resistance to EGFR-TKI, RECIST criteria, and the new lung cancer staging system, three clinical factors—the duration of disease control, evolution of tumor burden, and clinical symptom—were chosen as grouping variables [12,17,21,22]. Duration of disease control was the interval from baseline to the first documentation of PD. Evolution of tumor burden was represented by the volume doubling time (VDT) of target lesions and progressive involvement in non-target lesions between the two latest consecutive assessments. Progression in non-target lesions was defined as progression of pre-existing lesions, progression due to new lesions in the thoracic cavity, new lesions beyond the thoracic cavity, or new malignant effusion [22]. Each progression was scored as 1. Quantification of progressive involvement in non-target lesions was expressed as a score of 1–4. Clinical symptom was quantified based on six items: cough, hemoptysis, chest pain, fever, dyspnea and metastatic lesion related symptom [23]. Scores 0, 1 and 2 was quantified in accordance with the asymptomatic status, stability of pre-existing item, and deterioration of any pre-existing item or new item [24]. Factors including the duration of disease control, VDT of target lesions, and scaling of non-target lesions were analyzed in a three-dimensional scatter plot to establish a grouping model. Clinical symptom correlated with tumor burden, was incorporated into the model and verified by Bayes discriminant analysis. Clinical definitions of the dramatic, gradual, and local progression groups were approved to represent the results. Clinical factors, genetic variations, and subsequent treatment were also analyzed.

2.3. EGFR and c-MET profile

Mutations in exons 18–21 of the tyrosine kinase domain of the EGFR gene were detected in EGFR-TKI-naïve or TKI-resistant tumors using a polymerase chain reaction (PCR)-based direct sequencing method [1,25]. The c-MET copy number was assessed by quantitative relative real-time PCR in EGFR-TKI-resistant patients; gene amplification was defined according to literature [26,27].

2.4. Statistical analysis

Chi-square or Fisher's exact tests were used to compare qualitative data. PFS was defined as the time from commencement of EGFR-TKI to the first documentation of progressive disease (PD) or death from any cause. Post-progression survival (PPS) was defined as the interval from documentation of PD to the last visit or death from any cause [28]. OS was calculated from commencement of TKI to the last visit or death from any cause [29].

Kaplan–Meier method was used to estimate survival curves. Log-rank test was used to compare survival curves among patient groups. Multivariate Cox proportional hazards regression was used to evaluate independent prognostic factors associated with PFS or OS. All statistical tests were two-sided and $P < 0.05$ was deemed to be statistically significant.

3. Results

3.1. Definition of three failure modes

The 120 trial (training set) and 107 routine patients (validating set) were analyzed using three-dimensional scatter plots. In training set, median durations of disease control were 9.1, 12.5, and 7.6 months in the dramatic, gradual, and local progression groups, respectively; these differences were significant ($P = 0.001$). VDTs of the groups were 2.2, 13.4, and 6.9 months in the dramatic, gradual, and local progression groups, respectively; these differences were significant ($P < 0.001$). The percentages of patients with a progression score >2 in a specific group were 47.5% (28/59) in dramatic progression group, 23.3% (7/30) in gradual progression group, and 3.2% (1/31) in local progression group. The non-target lesion score was significantly different among the groups ($P < 0.001$; Fig. 1A). The following factors were also significantly different among the three groups in validating set: duration of disease control: $P = 0.02$; VDT: $P < 0.001$; and scores of non-target lesion: $P < 0.001$ (Fig. 1B). The mentioned three factors and clinical symptom in training set were analyzed in a Bayes discriminant analysis. Discriminant functions for different groups were as follows: dramatic progression group (Dis) $= -16.19 + 0.39X + 0.24Y + 3.50Z + 9.03S$ (symptom); gradual progression group (Dis) $= -16.82 + 0.51X + 0.98Y + 2.80Z + 5.30S$; and local progression group (Dis) $= -10.08 + 0.35X + 0.52Y + 1.26Z + 7.00S$. Data indicated a correct grouping rate of 87.9% in the validating set.

Quantification of symptom in dramatic progression group was significantly higher than gradual or local progression group ($P < 0.001$). Based on the above results, definitions of the three modes were approved (Table 1). The dramatic progression group demonstrated the shortest disease control, shortest VDT in target lesions, worst progressive involvement, and experienced symptom deterioration. The gradual progression group showed the longest disease control, longest VDT in target lesions, moderate progressive involvement, and persistent symptom benefit. The local progression group displayed moderate disease control, moderate VDT in target lesions, the most limited progressive involvement, and persistent symptom benefit.

3.2. Patient characteristics

EGFR-TKI failure in the 227-patient cohort was divided into three modes: 130 patients with dramatic progression (57.3%), 42

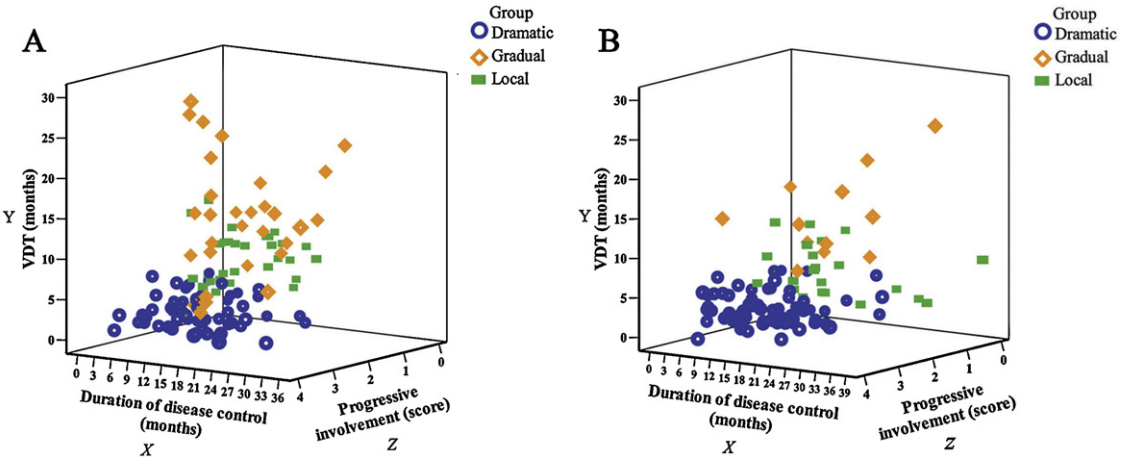

Fig. 1. Grouping model according to clinical factors. (A) One-hundred and twenty trial patients. (B) One-hundred and seven routine patients. The *X* axis (duration of disease control). The *Y* axis (volume doubling time, VDT) represents the growth rate of target lesions between the two latest consecutive assessments, and was calculated according to previous reports [21,30,31]. The *Z* axis (progressive involvement) refers to the extent of non-target lesion involvement.

with gradual progression (18.5%), and 55 with local progression (24.2%). Characteristics of patients among the three modes were balanced regarding gender, age, cigarette history, Eastern Cooperative Oncology Group performance status (ECOG PS), disease stage, histology, percentage of trials, and line of TKI (Table 2). A total of 57.7% of patients were female. Most patients (96.5%) were diagnosed with stage IV disease upon commencement of EGFR-TKI. The most common histologic subtype was adenocarcinoma (94.3%), and 49.3% of patients received first-line EGFR-TKI. For subsequent treatment of TKI-resistance, patients with gradual or local progression received continuation of TKI, but patients with dramatic progression were frequently switched to chemotherapy ($P < 0.001$).

3.3. EGFR mutation and c-MET amplification

EGFR mutations were analyzed in 82.8% (188/227) of TKI-naïve patients: 12.8% (24/188) of these had the wild-type gene, 1.1% (2/188) had the exon 18 mutation, 47.9% (90/188) had the exon 19 deletion, 1.1% (2/188) had the T790M mutation in exon 20, 36.7% (69/188) had the exon 21 point mutation, and 0.5% (1/188) had the exon 18 plus 21 double mutation. EGFR mutations in the TKI-naïve setting were well-balanced among the three groups ($P = 0.41$).

Detection of EGFR mutations was performed in 38.8% (88/227) of TKI-resistant patients; 28.4% (25/88) patients with T790M mutation were confirmed. The c-MET copy number was assessed in 12.3% (28/227) of TKI-resistant patients, and two patients (7.1%) with c-MET amplification were detected. The distribution of EGFR T790M mutation among the three groups was not significantly different ($P = 0.69$), neither was that of c-MET amplification ($P = 0.41$).

Table 1
Criteria for EGFR-TKI failure modes in NSCLC.

Mode	Criteria[a]
Dramatic progression	(1) Disease control lasting ≥3 months with EGFR-TKI treatment [14] (2) Compared with the previous assessment, rapid progression of multiple target lesions, or progressive involvement of non-target lesions with a score >2 [21,22] (3) Symptom scored 2
Gradual progression	(1) Disease control lasting ≥6 months with EGFR-TKI treatment [32,33] (2) Compared with the previous assessment, no significant increment of tumor burden and progressive involvement of non-target lesions with a score ≤2 [21,22] (3) Symptom scored ≤1
Local progression	(1) Disease control lasting ≥3 months with EGFR-TKI treatment [14] (2) PD due to solitary extracranial lesion or limitation in intracranial lesions (covered by a radiation field) [34–37] (3) Symptom scored ≤1

Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; PD, progressive disease.

[a] All conditions should be met.

3.4. Survival in different modes

The difference in the median PFS (mPFS) among the three groups was significant ($P = 0.007$; Fig. 2A). The mPFS of patients in gradual progression group (12.9 months; 95% confidence interval (CI): 10.9–14.8 months) was significantly longer than that in dramatic progression group (9.3 months; 95% CI: 8.6–10.1 months; $P = 0.001$) or local progression group (9.2 months; 95% CI: 7.4–11.0 months; $P = 0.011$). No significant difference was found regarding the mPFS between dramatic and local progression groups ($P = 0.955$). The difference in median PPS (mPPS) among the three groups was significant ($P < 0.001$; Fig. 2B). The mPPS of gradual progression group (18.4 months; 95% CI: 7.7–29.1 months) was significantly longer than that of local progression group (8.7 months; 95% CI: 7.5–9.9 months; $P = 0.04$). The mPPS of local progression group was significantly longer than that of dramatic progression group (5.1 months; 95% CI: 3.4–6.7 months; $P = 0.005$). For patients underwent only BSC after TKI failure, gradual progression group showed the longest mPPS ($P = 0.004$).

The median OS (mOS) among the three groups was significantly different ($P < 0.001$; Fig. 2C). Patients in gradual progression group demonstrated a longer OS (39.4 months; 95% CI: 24.2–54.5 months) compared with those in local progression group (23.1 months; 95% CI: 20.8–25.4 months; $P = 0.003$). Patients in local progression group displayed a significantly longer OS than those in dramatic progression group (17.1 months; 95% CI: 14.9–19.4 months; $P = 0.018$). Regarding subsequent treatment for TKI-resistance in patients with dramatic progression, the difference between TKI continuation and switching to chemotherapy showed marginal significance (18.6 months *vs.* 23.9 months; $P = 0.07$). In gradual progression group, TKI continuation demonstrated a significantly longer mOS than did switching to chemotherapy (39.4 months *vs.* 17.8 months; $P = 0.02$; Fig. 2D). The mOS was comparable between continuation of

Table 2
Patient demographics and clinical characteristics.

Group	Total	Dramatic progression		Gradual progression		Local progression		*P*
		n	%	*n*	%	*n*	%	
Gender								0.19
Male	96	51	39.2	23	54.8	22	40.0	
Female	131	79	60.8	19	45.2	33	60.0	
Age (years)								0.29[a]
Median (range)	58 (26–85)	60 (26–85)		59 (42–82)		55 (42–77)		
Smoking status								0.12
Never[b]	157	96	73.8	24	57.1	37	67.3	
Smoker	70	34	26.2	18	42.9	18	32.7	
ECOG PS								0.54[c]
≤2	221	125	96.2	42	100.0	54	98.2	
>2	6	5	3.8	0	0.0	1	1.8	
Stage								0.22[c]
III	8	3	2.3	1	2.4	4	7.3	
IV	219	127	97.7	41	97.6	51	92.7	
Histology								0.39[c]
ADC	214	123	94.6	41	97.6	50	90.9	
Non-ADC	13	7	5.4	1	2.4	5	9.1	
Line of TKI								0.67
1st	112	61	46.9	23	54.8	28	50.9	
≥2nd	115	69	53.1	19	45.2	27	49.1	
Subsequent treatment[d]								<0.001
Chemotherapy	66	47	36.2	8	19.0	11	20.0	
TKI	68	15	11.5	26	61.9	27	49.1	
BSC	93	68	52.3	8	19.0	17	30.9	
Total	227	130	100	42	100	55	100	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ADC, adenocarcinoma; TKI, tyrosine kinase inhibitor; BSC, best supportive care.
[a] Non-parametric test.
[b] Never smokers were defined as patients who had smoked less than 100 cigarettes in their lifetime.
[c] Fisher's exact test.
[d] Treatment following the first documentation of disease progression.

EGFR-TKI and chemotherapy in local progression group (23.6 months *vs.* 23.7 months; $P = 0.66$). For patients received only BSC after TKI failure, gradual progression group showed the longest mOS ($P = 0.001$).

3.5. Cox proportional hazards regression

To estimate the risk of PFS in the cohort of 227 patients, gender, age, cigarette smoking history, PS, disease stage, histology, line of TKI, failure modes, and EGFR mutation at baseline were used as covariates in a Cox proportional hazards regression model. The hazard ratio (HR) in patients of gradual progression group was significantly lower than that in dramatic (HR = 0.557; $P = 0.001$) or local (HR = 0.598; $P = 0.014$) progression groups. Additionally, the aforementioned factors were used as covariates in a stratified Cox model to evaluate the benefit of OS. A survival benefit was observed in gradual progression group compared with dramatic (HR = 0.266; $P < 0.001$) or local progression group (HR = 0.429; $P = 0.007$). Furthermore, the risk of death in local progression group was lower than that in dramatic progression group (HR = 0.621; $P = 0.018$).

4. Discussion

Our data indicated that diversity of EGFR-TKI failure could be divided into three modes based on the duration of disease control, evolution of tumor burden, and clinical symptom, regardless of genotype profile. Length of disease control was closely related to prognosis [14,32,33]. Thus, incorporating the duration of disease control into the grouping criteria was reasonable. Tumor response was evaluated according to RECIST in routine practice or clinical trials. Assessment of overall tumor burden was accomplished by documentation of target and non-target lesions. Evaluation of PD was based on a comparison of the latest follow-up and recorded best response [21]. However, the RECIST criteria could not reflect the diversity of failure in patients with EGFR-TKI treatment, possibly resulting in discontinuation of TKI. In our proposed grouping criteria, the previous assessment, instead of the best response, was taken as a reference. Determination of tumors with dramatic or gradual progression was challenging. Thus, the VDT was introduced as a parameter for assessing the growth characteristics of lesions. Lung cancers with a longer VDT were associated with better prognosis [30,31]. We calculated VDT in target lesions to assess the growth rate of tumors. Patients with different length of VDTs were categorized into different groups. Patients with a relatively longer VDT were assigned to gradual progression group. Our study measured non-target lesions using a scaling system because the extent of progressive involvement had prognostic impact [22]. Patients with dramatic progression demonstrated higher scores, which represented rapid growth of tumor burden. Patients with local progression scored the lowest in measurement of non-target lesions, and displayed the most limited progressive involvement, which could be covered by a radiation field. Different failure modes demonstrated diverse symptom measurement; incorporation of symptom evaluation made the grouping model could be more comprehensive. The rate of accordance in grouping between discriminant function and proposed criteria achieved 87.9% in validation. Because the molecular mechanism of EGFR-TKI failure was not elucidated fully, and no genotype-directed subsequent management was established, classification of failure modes by the proposed criteria required only clinical observations and radiological assessment, which suggested its feasibility and practicability in clinical practice, design of trials, or communication with patients.

ECOG PS, gender, and EGFR mutation status for each treatment group within each failure mode were well balanced (Supplementary data, Tables S1–S3). Survival analysis suggested that mPFS was significantly longer in gradual progression group than in dramatic or local progression groups. The mPPS and mOS were significantly longer in gradual progression group than in dramatic or local progression groups, respectively. The mPPS and mOS were also significantly longer in local progression group than in

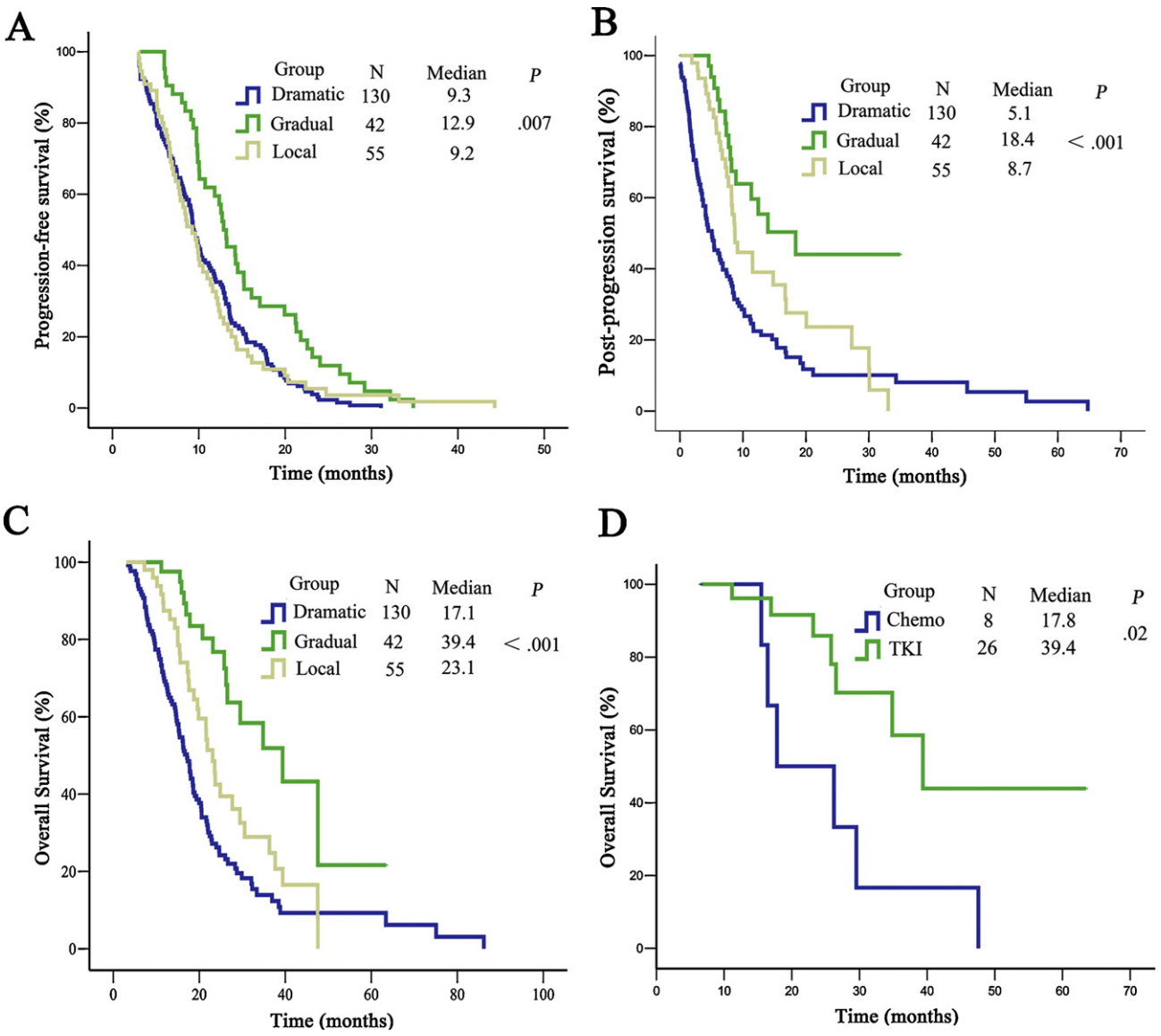

Fig. 2. Kaplan–Meier curves of patients in different groups. (A) Progression-free survival. (B) Post-progression survival. (C) Overall survival in patients of different groups. (D) Overall survival in the gradual progression group with different subsequent treatments.

dramatic progression group. To our knowledge, this is the first study to show that EGFR-TKI failure modes have prognostic value in advanced NSCLC. Clinical modes of failure may serve as an extension and supplement to the clinical definition of acquired resistance proposed by Jackman et al. [12]. Although resistance acquired through the T790M mutation may follow a more indolent course than clinical resistance without the mutation [17,28,38], patients with gradual progression in our study also had a significantly longer survival, regardless of T790M mutational status. Clinically, the definition of gradual progression might indicate both an indolent course and a favorable prognosis much better than T790M mutation. Given the indolent nature of T790M-mediated resistance, continued EGFR-TKI administration is appropriate for those with the T790M mutation despite progression [28,39].

Our data showed that patients in dramatic progression group demonstrated a better survival with switching to chemotherapeutic regimens instead of continued TKI therapy. Because those patients demonstrated deteriorated symptom on TKI treatment, TKI discontinuation seemed to be a reasonable choice in clinical practice. For patients with gradual progression, continuation of EGFR-TKI achieved significantly longer mOS than those receiving subsequent chemotherapy. Thus, for those with gradual progression in clinical practice, continuation of EGFR-TKI would be an optimal treatment strategy after failure. Retrospective studies reported continuation of systemic treatment may still produce benefit after local relapse [14,40,41]. In our analysis, for patients with local progression, continuation of EGFR-TKI was comparable to chemotherapy as subsequent treatment in terms of mOS. Because those patients experienced persistent clinical benefit from EGFR-TKI, the "*in vivo* drug test" supported TKI continuation in this setting because switching to chemotherapy may affect the quality of life in advanced patients [2,42]. Patients with local progression demonstrated strictly localized lesions, so continuation of EGFR-TKI as systemic treatment plus local intervention was rational in clinical practice. Up to now, there were no established treatment modes after EGFR-TKI failure. We determined subsequent treatment based on clinical observations and medical literature in the retrospective study [2,6,14,28]. Trials including ASPIRATION [43] and IMPRESS (NCT01544179) are ongoing to explore the treatment strategies for EGFR-TKI failure. Continuing TKI plus chemotherapy

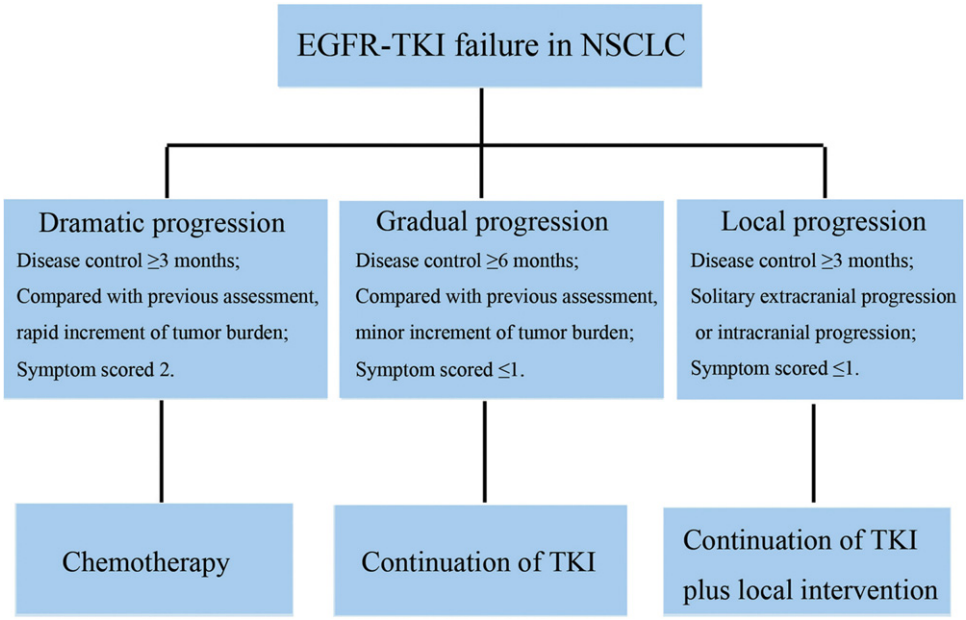

Fig. 3. Clinical management of different EGFR-TKI failure modes. EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; NSCLC, non-small cell lung cancer.

might be a potential strategy beyond progression, and the algorithm will be answered by trial IMPRESS. Based on the available data, we propose strategies for clinical management of different EGFR-TKI failure modes (Fig. 3). A prospective study with 226 cases at our center will be conducted to investigate the strategy of management.

The present study possesses intrinsic limitations due to its retrospective design, including lack of a control arm and prospective sample size estimation. Second, EGFR mutation status was unknown in 17.2% (39/227) of the cohort, and only 38.8% (88/227) with acquired resistance underwent re-biopsy and detection of molecular profile. The present data failed to uncover the inherent molecular mechanism of diverse TKI failure modes. Potential mechanisms may correlate with secondary gene variations or mixed response induced by tumor heterogeneity [44]. Finally, the regimens used for treating resistance were not designed in a randomized control manner. A total of 52.3% patients with dramatic progression and 30.9% with local progression underwent BSC after TKI-resistance; this may interfere with results and underestimate the potential role of failure modes in subsequent strategy formulation.

In conclusion, the diversity of EGFR-TKI failure could be categorized into three modes according to specific criteria derived from clinical factors. Determination of clinical modes could favor strategies for subsequent treatment and prediction of prognosis. Further investigation of the underlying molecular mechanism is warranted to elucidate the EGFR-TKI failure modes in advanced NSCLC.

Author contributions

Conception and design was done by Jin-Ji Yang, Hua-Jun Chen, Hong-Hong Yan, Yi-Long Wu. Jin-Ji Yang, Hua-Jun Chen, Hong-Hong Yan provided the study materials or patients. Hong-Hong Yan, Xu-Chao Zhang, Qing Zhou, Jian Su, Zhen Wang, Chong-Rui Xu, Yi-Sheng Huang, Bin-Chao Wang, Xue-Ning Yang, Wen-Zhao Zhong, Qiang Nie, Ri-Qiang Liao, Ben-Yuan Jiang and Song Dong collected and assembled the data. Data analysis and interpretation were done by Hong-Hong Yan, Xu-Chao Zhang, Chong-Rui Xu. Manuscript was written and finally approved by all authors.

Role of funding source

The sponsors did not have any role in the design of the study; collection, analysis, and interpretation of the data; writing of the report; or in the decision to submit for publication. Yi-Long Wu had full access to all the data and had final responsibility for the decision to submit for publication.

Conflict of interest statement

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

Acknowledgments

This work was supported by the National Natural Science Foundation of China, Grant No. 30772531; Guangdong Science and Technology Department, Industry Technology Research and Development Projects, Grant No. 2011A030400010 and Guangzhou Science and Information Technology Bureau, Grant No. 2011Y2-00014 (Y.-L.W.).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2012.09.016.

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