RESEARCH ARTICLE

Subsequent Treatment Choices for Patients with Acquired Resistance to EGFR-TKIs in Non-small Cell Lung Cancer: Restore after a Drug Holiday or Switch to another EGFR-TKI?

Tao Song[1], Wei Yu[1], Shi-Xiu Wu[2]*

Abstract

The outcomes of first-generation EGFR-TKIs (Gefitnib and Erlotinib) have shown great advantages over traditional treatment strategies in patients with non-small cell lung cancer (NSCLC), but unfortunately we have to face the situation that most patients still fail to respond in the long term despite initially good control. Up to now, the mechanism of acquired resistance to EGFR-TKIs has not been fully clarified. Herein, we sought to compile the available clinical reports in the hope to better understanding the subsequent treatment choices, particularly on whether restoring after a drug holiday or switching to another EGFR-TKI is the better option after failure of one kind of EGFR-TKI.

Keywords: Non-small cell lung cancer (NSCLC) - EGFR-TKIs - gefitnib - erlotinib - acquired resistance - failure

Asian Pac J Cancer Prev, **15 (1)**, 205-213

Introduction

Lung cancer is the most common cancer and the leading cause of cancer-related mortality worldwide. Conventional chemotherapeutic agents were associated with significant toxicity and less effective for advanced non-small cell lung cancer (NSCLC). There is a tendency that the benefits derived from chemotherapy had reached a plateau (Laack et al., 2010). The recommended first-line therapy of a platinum-based doublet had an objective response rate of only approximately 20% and a median survival time of 8–10 months for patients with stage IIIB or IV disease (Schiller et al., 2002) and no particular combination regimen offering a significant advantage over each other. The second-line chemotherapy of docetaxel and pemetrexed had response rates (RR) of only 8%–9% with progression-free survival (PFS) of less than 3 months (Hanna et al., 2004).

EGF (epidermal growth factor) plays an important role in the erb-B signalling pathway which could promote cancer cell proliferation and tumor invasion and EGFR (epidermal growth factor receptor) is one of four structurally related members of the erb-B family of transmembrane tyrosine kinases; Over expression of EGFR is common in NSCLC and is associated with a poorer outcome (Volm et al., 1998; Ohsaki et al., 2000); As first-line setting, Gefitinib had been reported with promising results in Asian countries in a multicentre phase III randomized clinical trial which suggested that Gefitinib might be a good option for first-line treatment of adenocarcinoma in non-smoking Asians with superior clinical efficacy and tolerability compared to standard chemotherapy (Fukuoka et al., 2011); Similar to the findings of Gefitinib, two randomized phase III studies demonstrated that Erlotinib achieved a better PFS and a higher response rate compared to chemotherapy as first-line treatment in patients with the EGFR mutation (Rosell et al., 2011; Zhou et al., 2011). As second and third-line treatment of advanced NSCLC, Gefitinib and Erlotinib also showed survival advantage and better quality of life than traditional chemotherapies in a series of clinical trials. But unfortunately, the majority of patients receiving Gefitnib or Erlotinib would inevitably develop resistance after 6 months treatment, which were characterized by the presence of a known additional T790M mutation located in exon 20 (Sequist et al., 2007; Sequist et al., 2008) or the amplification of MET responsible for up to 20% of relapsing patients (Bean et al., 2007; Laack et al., 2010). The lack of an established therapeutic option for NSCLC patients who have progressive disease after EGFR-TKIs failure poses a great challenge to physicians in terms of how best to manage this growing group of patients. Based on these backgrounds, the purpose of this review is to compile the published reports dealing with the subsequent treatment strategies especially on restoring after a drug holiday and switching to Gefitnib or Erlotinib for acquired resistance to EGFR-TKIs.

Materials and Methods

Search strategy and criteria for selecting studies

The literature search was conducted with assistance

[1]*Department of Radiation Oncology, The First Clinical College of Wenzhou Medical University, Hangzhou Cancer Hospital,* [2]*Department of Radiation Oncology, Hangzhou Cancer Hospital, Hangzhou, China *For correspondence: wushixiu@medmail.com.cn*

Table 1. Characteristics of the Published Reports of Retreated with Gefitnib or Erlotinib Following a Drug Holiday

	Author (reference)	No. of patients	Country of origin	Study design	Gender (F/M)	ECOG PS (0-1/2-4)	Histology (AC/SQC/other)	Smoking (yes[a]/no)	EGFR mutation (+/-/unknown)
Gefitnib	Oh et al.	23	Japan	Prospective	20/3	17/6	22/1/0	2/21	13/1/9
	Koizumi et al.	20	Japan	Prospective	17/3	14/6	20/0/0	2/18	-
	Asahina et al.	16	Japan	Prospective	13/3	14/2	14/1/1	5/11	3/3/10
	Watanabe et al.	3	Japan	Retrospective	3/0	-	3/0/0	1/2	1/0/2
	Tomizawa et al.	20	Japan	Retrospective	17/3	18/2	20/0/0	5/15	-
	Yokouchi et al.	27	Japan	Retrospective	-	-	-	-	-
	Yano et al.	3	Japan	Case report	2/1	2/1	3/0/0	0/3	-
	Yoshimoto et al.	1	Japan	Case report	0/1	-	0/0/1	1/0	-
	Kurata et al.	1	Japan	Case report	0/1	1/0	1/0/0	-	-
	Guo et al	1	China	Case report	1/0	-	1/0/0	0/1	-
	Li et al.	1	China	Case report	1/0	1/0	1/0/0	0/1	-
Erlotinib	Faehling et al.	25	Germany	Retrospective	16/9	22/3	23/1/1	6/19	9/6/10
	Becker	14b	Netherland	Retrospective	9/4	-	-	-	12/0/2
	Guo et al.	1	China	Case report	1/0	-	1/0/0	0/1	-
Tatal		156			100/28	89/20	109/3/3	22/92	38/10/43

Note: G, gefitinib; E, erlotinib; F, female; M, male; ECOG PS, Eastern Cooperative Oncology Group performance status; AC, adenocarcinoma; SQC, squamous cell carcinoma; EGFR, epidermal growth factor receptor; a: including patients who were quit smoking for years; b: one patient treated with sorafenib as first TKI treatment, another one treated with Gefitinib as first TKI treatment, three patients combined erlotinib with cetuximab as second TKI treatment

from a research librarian in the database of PubMed, Embase and Google Scholar to identify all clinical trials and case reports that contained advanced or metastatic NSCLC patients gained acquired resistance after treated with Gefitnib or Erlotinib and subsequently retreated with TKIs, we did not restrict Gefitnib or Erlotinib as first-line setting or subsequent treatment choices. The search strategy included articles from January 2004 to June 2013 indexed under the keywords of "Erlotinib or Gefitinib failure or EGFR TKI failure and lung cancer". The title and abstract of studies identified in the search were reviewed to exclude studies that did not answer the research question. The search did not restrict the type of publication or periodical. We selected all published reports that clearly described the following therapies that were administered with advanced or metastatic NSCLC patients who had documented progressive disease after treated with Gefitinib or Erlotinib. When complete information was not available, attempts were made to contact the corresponding authors of the studies for additional information. Furthermore, the search was only limited to English language (Kaira et al., 2010).

Review Methods

The abstracts of articles were reviewed by our corresponding author. Irrelevant citations were removed according to the criteria mentioned above, thus creating a preliminary set of potentially relevant publications. Secondly, the full text articles were distributed to the two reviewers along with an evaluation form customized for reviewing the following therapies after acquired resistance to EGFR-TKIs; Two reviewers independently evaluated a number of allocated articles and extracted information regarding study design, study population, interventions, methods, outcome measures, results and conclusions for each article. The evaluation results were compared and re-evaluated until consensus was reached between two reviewers (Jensen et al., 2010).

Results

Retreat with Gefitnib or Erlotinib following a drug holiday

It had been observed that some patients with EGFR-mutation positive NSCLC who developed resistance to Gefitinib or Erlotinib had accelerated progression of disease after discontinuation of TKI (Chaft et al., 2011; Pallis and Syrigos, 2013). This phenomenon suggested that some tumor cells may still remain sensitive to EGFR-TKIs. We summarized 14 identified clinical reports about retreated with Gefitnib or Erlotinib following a drug holiday (Table 1).

We excluded one paper due to no report of using Gefitnib or Erlotinib (Riely et al., 2007). Of these 156 patients, 117 (75.0%) were Asian and 39 (25.0%) were Caucasian. 100 patients (64.1%) were women and 56 (35.9%) were men. Performance status (PS), histology of the patients and smoking history were as follows: PS 0-1 (89/109, 81.7%), PS 2-4 (20/109, 18.3%); adenocarcinoma (109/115, 94.8%), squamous cell carcinoma (SQC) (3/115, 2.6%), other (3/115, 2.6%); smoker (22/114, 19.3%), non-smoker (92/114, 80.7%). Because EGFR mutation testing was approved relatively later than the administration of EGFR-TKIs in some countries, only 91 (58.3%) of 156 patients had tested EGFR mutations, and EGFR mutations were detected in 38 (41.8%) of 91 patients. In all of these 38 patients, the EGFR mutations were examined in the tumor samples prior to initiation of EGFR-TKIs therapy. Table 2 shows the response rate to Gefitnib or Erlotinib after following a drug holiday of initial EGFR-TKI, For these prospective or retrospective studies, only those benefit from prior Gefitnib or Erlotinib could enter the study and receive a second course of EGFR-TKI, so the disease control rate was 100.0% at first, and in the second course ,there was observed in (27/127) 21.3% in PR, (44/127) 34.6% in SD and (56/127) 44.1% in PD, the disease control rate of second course of EGFR-TKI was 55.9%. Median Time-to-Progression (TTP) to initial

Table 2. Response to Gefitnib or Erlotinib Following a Drug Holiday and Time from Initial TKI to Retrement and Therapies Between EGFR-TKIs

	Author (reference)	No. of patients	Response to prior EGFR-TKI PR (%)	SD (%)	PD (%)	Response to sceond EGFR-TK PR (%)	SD (%)	PD (%)	* median	** median	***
Gefitnib	Oh et al.	23	8	15	-	5	10[d]	5	9.1	7.0	C
	Koizumi et al.	20	17	3	-	3	6	11	13.9(PR) and 8.0(SD)	13.0	C
	Asahina et al.	16	16	0	-	-	7[d]	8	-	-	C
	Watanabe et al.	3	-	3[a]	-	1	1	1	-	-	C
	Tomizawa et al.	20	16	4	-	5	8	7	11.0	7.2	C
	Yokouchi et al.	27	27	0	-	5	-	22	-	-	R, C, BSC
	Yano et al.	3	1	2	-	0	3	-	12.3	8.7	R, C
	Yoshimoto et al.	1	1[b]	-	-	1	-	-	12.0	5.0	R, C
	Kurata et al.	1	1[c]	-	-	1	-	-	18.0	11.0	C
	Guo et al	1	1	-	-	-	1	-	29.0	1.0	R, C
	Li et al.	1	1	-	-	-	1[e]	-	15.0	5.0	R, C
Erlotinib	Faehling et al.	25	20[f]	5	-	-	-	-	15.5	-	R, C, BSC
	Becker	14	14	-	-	5	7	2	12.5	9.5	C
	Guo et al.	1	1	-	-	1	-	-	12.0	4.0	C
Total		156	124(79.5%)	32(20.5%)		27(21.3%)	44(34.6%)	56(44.1%)			
DCR				100.0%			55.9%				

Note, G, gefitinib; E, erlotinib; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate; a, Reported only the disease control rate (as the sum of PR and SD); b, CR; c, This patient took gefitinib 700 mg/d at initiation of treatment and got CR; d, a total of 4 cases of unavailable; e, This patient took gefitinib 500 mg/d at readministration of treatment; f, including one case of CR; C, chemothreapy; R, radiotherapy; BSC, best supportive care; *, "TTP to initial TKI therapy(m); **, Time from progression on initial TKI to retreatment(m); ***, Therapies between EGFR-TKIs

TKI therapy was also investigated in the identified 110 patients, except (Yokouchi et al., 2007; Asahina et al., 2010; Watanabe et al., 2011), and it ranged from 8.0 to 29.0 months for TKI therapy and 1.0 to 13.0 months for time from progression on initial TKI to retreatment, during the drug holiday, all patients received chemotherapy, radiotherapy and best supportive care (BSC) only played a role as adjuvant treatment for bone/brain metastases.

Switch between Erlotinib and Gefitinib.

Up to now, the best management of patients with acquired resistance to EGFR-TKIs remains unclear, except the above treatment option, it has been suggested that Erlotinib and Gefitinib should have similar effects because of their similar structures and mechanisms, but some differences between these two TKIs have also been demonstrated in pharmacodynamics and clinical settings. So we consider to compiling available clinical reports about switching between Erlotinib and Gefitinib.

Table 3 summarized the 24 identified clinical reports. When we collected articles, we found that Kaira and his colleagues had already published an article on this topic (Kaira et al., 2010) in 2010, so our team decided to do a more comprehensive summary on the basis of their work. First, our review group updated reports from Zhou et al. (2009) to Kim et al. (2008) based on the topic about replacing Erlotinib to Gefitinib and then added two papers about switching to Gefitinib after Erlotinib failure based on our search criteria. Of these 445 patients, 398 (89.4%) were Asian and 47 (10.6%) were Caucasian. 268 patients (60.2%) were women and 177 (39.8%) were men. We can see an obvious tendency that East Asian countries especially Japan invested their enormous enthusiasm; just like the treatment option mentioned above, the Japanese experts did a great number of clinical researches in this area basically. Performance status (PS), histology of the patients and smoking history were as follows: PS 0-1 (205/363, 56.5%), PS 2-4 (158/363, 43.5%); adenocarcinoma (362/415, 87.2%), squamous cell carcinoma (SQC) (17/415, 4.1%), other (36/415, 8.7%); smoker (149/390, 38.2%), non-smoker (241/390, 61.8%). and EGFR mutations (+) were detected in 170 (44.5%) of 382 patients.

In the replacement therapy after failure of one kind of TKI, there was observed (33/403) 8.2% in PR, (141/403) 35.0% in SD and (229/403) 56.8% in PD (Table 4).

Table 5 shows the response to the other EGFR-TKI after failure of one kind of TKI with or without EGFR mutation and median PFS or TTP of the replacement therapy. 145 patients had EGFR mutations. Response to the second course of TKI was observed in 5/145 (3.4%) in PR, 67/145 (46.2%) in SD and 73/145 (50.4%) in PD. Disease control rate was 49.7% for the replacement therapy. On the other hand, in 116 patients who had a wild type EGFR, response to the other TKI was observed in 5/116 (4.3%) in PR, 35/116 (30.2%) in SD and 76/116 (65.5%) in PD. Disease control rate was 34.5% for the treatment. No significant difference of disease control rate (49.7% vs 34.5%, $p = 0.411$) and response rate (3.4% vs 4.3%, $p = 0.184$) was observed between patients with EGFR mutations and patients with wild type EGFR. Given two papers (Luo et al., 2012; Zhou et al., 2009) use the item of "Time-to-Progression (TTP)" to calculate the efficiency of treatment duration, we put the TTP and PFS together to facilitate the compile and do not compare the P value of this part statistically; Median PFS or TTP was investigated in the identified 332 patients and it ranged from 5.9 to 17.0 months for Gefitinib therapy and from 1.7 to 5.9 months for Erlotinib therapy. The duration of PFS/TTP of these new updated papers didn't break through the time of the primary report by Kaira and his colleagues.

Table 3. Characteristics of the Published Reports of Switching Between Erlotinib and Gefitinib in NSCLC

	Author (reference)	No. of patients	Country of origin	Study design	Gender (F/M)	ECOG PS (0-1/2-4)	Histology (AC/SQC/other)	Smoking (yes[a]/no)	EGFR mutation (+/-/unknown)
G→E	Cho et al.	21	Korea	Prospective	11/10	6/15	16/3/2	10/11	5/12/4
	Vasile et al.	8	Italy	Prospective	4/4	5/3	6/0/2	1/7	NR
	Lee et al.	23	Korea	Prospective	19/4	12/11	22/0/1	NR	5/5/13
	Sim et al.	16	Korea	Retrospective	16/0	2/14	16/0/0	0/15	5/5/6
	Wong et al.	14	Singapore	Retrospective	10/4	NR	10/1/3	1/13	8/6/0
	Costa et al.	13	USA	Retrospective	9/4	NR	11/0/2	5/8	13/0/0
	Gridelli et al.	3	Italy	Case report	3/0	NR	3/0/0	0/3	NR
	Viswanathan et al.	5	USA	Case report	4/1	NR	NR	NR	NR
	Chang et al.	1	Taiwan	Case report	0/1	NR	1/0/0	1/0	1/0/0
	Walther et al.	1	UK	Case report	1/0	NR	1/0/0	0/1	NR
	Garfield	1	USA	Case report	0/1	0/1	0/0/1	1/0	NR
	Zhou et al.	21	China	Retrospective	7/14	1/20	8/9/4	10/11	7/14/0
	Wong et al.	21	Hong Kong	Retrospective	19/2	19/2	19/0/2	1/20	3/1/17
	Asami et al.	42	Japan	Retrospective	29/13	24/18	42/0/0	14/28	29/13/0
	Saito et al.	21	Japan	Retrospective	12/9	19/2	19/0/2	9/12	12/1/8
	Song et al.	20	China	Retrospective	11/9	17/3	18/0/2	5/15	NR
	Hata et al.	125	Japan	Retrospective	76/49	88/37	117/0/8	55/70	63/28/34
	Luo et al.	29	China	Retrospective	11/18	0/29	26/0/3	20/9	6/13/10
	Shoji et al.	1	Japan	Case report	0/1	NR	1/0/0	NR	0/1/0
	Watanabe et al.	8	Japan	Retrospective	5/3	NR	7/1/0	3/5	2/0/6
	Shih et al.	25	Taiwan	Retrospective	12/13	NR	NR	NR	NR
	Kim et al.	10	Korea	Retrospective	7/3	NR	9/0/1	2/8	10/0/0
E→G	Grossi et al.	15	Italy	Prospective	1/14	12/3	9/3/3	11/4	0/14/1
	Choong et al.	1	USA	Case report	1/0	NR	1/0/0	0/1	1/0/0
	Total	445			268/177	205/158	362/17/36	149/241	170/113/99

Note: G, Gefitinib; E, Erlotinib; ECOG PS, Eastern Cooperative Oncology Group performance status; AC, adenocarcinoma; SQC, squamous cell carcinoma; EGFR, epidermal growth factor receptor; USA, United States of America; UK, United Kingdom

Table 4. Response to the Other TKI after Failure of Prior TKI

	Author (reference)	No. of patients	Response to prior TKI			Response to the other TKI		
			PR (%)	SD (%)	PD (%)	PR (%)	SD (%)	PD (%)
G→E	Cho et al.	21	6(28.6%)	4(19.0%)	11(52.4%)	2(9.5%)	4(19.0%)	15(71.5%)
	Vasile et al.	8	4(50.0%)	4(50.0%)	-	2(25.0%)	3(37.5%)	3(37.5%)
	Lee et al.	23	15(65.2%)	2(8.7%)	6(26.1%)	1(4.3%)	1(4.3%)	21(91.4%)
	Sim et al.	16	9(56.3%)	2(12.5%)	5(31.2%)	1(6.3%)	3(18.7%)	12(75.0%)
	Wong et al.	14	-	9[a](64.3%)	5(35.7%)	-	5[a](35.7%)	9(64.3%)
	Costa et al.	13	11(84.6%)	2(11.1%)	0(0.0%)	1(5.5%)	2(15.4%)	10(76.9%)
	Gridelli et al.	3	-	3(100%)	-	1(33.3%)	2(66.7%)	-
	Viswanathan et al.	5	-	4[a](80.0%)	1(20.0%)	-	-	5(100%)
	Chang et al.	1	1(100%)	-	-	1(100%)	-	-
	Walther et al.	1	-	-	1(100%)	1(100%)	-	-
	Garfield	1	-	-	1(100%)	1(100%)	-	-
	Zhou et al.	21	2(9.5%)	8(38.1%)	11(52.4%)	2(9.5%)	4(19.0%)	15(71.4%)
	Wong et al.	21	-	18[a](85.7%)	3(14.3%)	-	12(57.1%)	9(42.9%)
	Asami et al.	42	22(52.4%)	17(40.5%)	3(7.1%)	1(2.4%)	24(57.1%)	17(40.5%)
	Saito et al.	21	16(76.2%)	5(23.8%)	-	2(9.5%)	6(28.6%)	13(61.9%)
	Song et al.	20	5(25.0%)	9(45.0%)	6(30.0%)	-	7(35.0%)	13(65.0%)
	Hata et al.	125	68[b](54.4%)	22(17.6%)	28(22.4%)	11(8.8%)	44(35.2%)	70(56.0%)
	Luo et al.	29	11(37.9%)	14(48.3%)	4(13.8%)	3(10.3%)	12(41.4%)	14(48.3%)
	Shoji et al.	1	-	-	1(100%)	1(100%)	-	-
	Watanabe et al.	8	-	8[a](100.0%)	-	-	1(12.5%)	7(87.5%)
	Kim et al.	10	-	9[a](90.0%)	1(10.0%)	1[c](10%)	5(50.0%)	3(30.0%)
E→G	Grossi et al.	15	1(6.7%)	5(33.3%)	9(60.0%)	0(0.0%)	6(40.0%)	6[d](40.0%)
	Choong et al.	1	1(100%)	-	-	1(100%)	-	-
	Total	420	172(41.6%)	145(35.1%)	96(23.2%)	33(8.2%)	141(35.0%)	229(56.8%)
	Disease control rate			76.8%			43.2%	

Note, G, Gefitinib; E, Erlotinib; PR, partial response; SD, stable disease; PD, progressive disease.a, Reported only the disease control rate (as the sum of PR and SD); b, including 3 cases of CR and 4 cases of unknown; c, 1 case of CR; d, 3 cases of unknown

Combined with Radiotherapy

After acquired resitance to EGFR-TKIs, the majority of patients received chemotherapy, although there was a lot of difference between the chemotherapies, but encouraging results had only been obtained in some small sample of clinical trials. Local therapy is not commonly

Table 5. Response to the Other TKI after Failure of prior TKI in NSCLC with or Without EGFR Mutation and TTP or PFS of the Replacement Therapy

	Author	No. of	EGFR mutation (+)			No. of	EGFR mutation (-)			*	**
	(reference)	patients	PR (%)	SD (%)	PD (%)	patients	PR (%)	SD (%)	PD (%)	Total	Total
G→E	Cho et al.	5	–	1 (20.0%)	4 (80.0%)	12	2 (16.7%)	2 (16.7%)	8 (66.6%)	–	4.0
	Vasile et al.	–	–	–	–	–	–	–	–	17.0	5.9
	Sim et al.	5	–	2 (40.0%)	3 (60.0%)	5	–	1 (20.0%)	4 (80.0%)	6.3	1.7
	Wong et al.	8	–	5a (62.5%)	3 (37.5%)	6	–	–	6 (100%)	–	–
	Costa et al.	13	1 (7.7%)	2 (15.4%)	10 (76.9%)	–	–	–	–	–	–
	Chang et al.	1	1 (100%)	–	–	–	–	–	–	–	–
	Zhou et al.	7	–	2a(28.6%)	5(71.4%)	14	–	4(28.6%)	10(71.4%)	–	1.8
	Wong et al.		–	–	–	–	–	–	–	5.9	3.7
	Asami et al.	29	1(3.4%)	17(58.6%)	11(38.0%)	13	–	7(53.8%)	6(46.2%)	8.1	3.4
	Song et al.	5	–	–	5(100%)	10	–	5(50.0%)	5(50.0%)	9.2	1.0
	Hata et al.	63	–	32a(50.8%)	31(49.2%)	28	–	6a(21.4%)	22(78.6%)	7.6	2.0
	Luo et al.	6	1(16.7%)	4(66.6%)	1(16.7%)	13	2(15.4%)	4(30.8%)	7(53.8%)	–	3.0
	Shoji et al.	–	–	–	–	1	1(100%)	–	–	–	–
	Watanabe et al.	2	–	2(100%)	–	–	–	–	–	–	–
E→G	Grossi et al.	–	–	–	–	14	–	6(42.9%)	8(57.1%)	–	2.3
	Choong et al.	1	1 (100%)	–	–	–	–	–	–	–	–
	Total	145	5/145(3.4%)	67/145(46.2%)	73/145(50.4%)	116	5/116(4.3%)	35/116(30.2%)	76/116(65.5%)		
	DCR			49.7%				34.5%			

Note: G,Gefitinib; E, Erlotinib;DCR, disease control rate; PR, partial response; SD, stable disease; PD, progressive disease; PFS, Progression-free survival; TTP, Time to Progression; *, Median PFS or TTP of gefitinib (months); **, Median PFS or TTP of erlotinib (months)

used in metastatic lung cancer. Although some case reports and retrospective studies indicated potential benefit by surgical resection or radiation therapy for oligo-metastatic disease, specifically within the lung, adrenal gland or central nervous system (CNS) (Pfannschmidt et al., 2005; Voltolini et al., 2010; Yano et al., 2010), but other study did not support this opinion (Downey et al., 2002). Based on this paradox, we compiled the literature within the latest five years, In 2011, Shukuya et al. reported the efficacy of continuous EGFR-TKI administration following radiotherapy for isolated CNS failure (Shukuya et al., 2011), 17 NSCLC patients showed isolated CNS failure after clinical benefits (PR or SD longer than 6 months) from EGFR-TKIs and continuously received EGFR-TKIs following radiotherapy (whole brain radiotherapy or stereotactic radiotherapy) to the CNS metastases, The RR (response rate) and DCR of CNS lesions were 41% and 76%, respectively. And the median PFS, extracranial progression free survival and the median OS (overall survival) time were 80 days, 171 days and 403 days respectively; they concluded that continuous administration of EGFR-TKI after the determination of PD in isolated CNS metastasis and radiotherapy for the CNS metastasis might represent an effective treatment option. Another trial conducted by Marquez-Medina et al. reported the efficacy of continued Erlotinib maintenance and salvage radiation for solitary metastasis in NSCLC (Marquez-Medina et al., 2013), 30 patients were divided into two patterns (4 patients were enrolled into solitary-progression and 26 patients in the generalized-progression), all four cases with solitary progression did benefit from continued Erlotinib maintenance and salvage radiation with 41–140 % prolongation of PFS. It was reflected in an improved OS when they were compared with patients with generalized progression (76.4 vs. 19.9 months; $p = 0.018$). They concluded that continued Erlotinib maintenance and local salvage radiation is feasible and could contribute to a better outcome in selected NSCLC patients with solitary-progression to Erlotinib. Another report from Weickhardt et al. (2012) had reported the feasibility of salvage local therapy and target therapy maintenance to treat cranial and extra-cranial oligo-progressions in 15 ALK-positive crizotinib-treated and 10 EGFR mutant TKI-treated NSCLC patients. Adrenalectomy was applied to one of them, and radiation to the rest. Median PFS benefit was 6.2 months, and it was higher in patients with extra-cranial progression only (7.1 vs. 4 months; $p = 0.26$). Latest, The Memorial Sloan-Kettering Cancer Center had published a report (Yu et al., 2013) of local therapy (13 patients with surgical resection, 2 patients with radiofrequency ablation and 3 patients with radiation) with continued EGFR-TKI in EGFR mutant advanced lung cancers that have developed acquired resistance to EGFR-TKIs, The median TTP after local therapy was 10 months (95% CI: 2–27 months). The median time until a subsequent change in systemic therapy was 22 months (95% CI: 6–30 months). The median OS from local therapy was 41 months (95% CI: 26–not reached).They concluded that EGFR-mutant lung cancers with acquired resistance to EGFR-TKI therapy are amenable to local therapy to treat oligo-metastatic disease when used in conjunction with continued EGFR inhibition. Local therapy followed by continued treatment with an EGFR-TKI is well tolerated and associated with long PFS and OS. It is worth mentioning that the reports mentioned above were all retrospective analysis with small samples, a prospective randomized clinical trial is strongly warranted to validate such therapeutic approaches with defined treatment criteria to minimize bias.

Treat with second-generation TKIs.

The number of second-generation TKIs continues to grow, with new reversible and irreversible members of the class under preclinical or clinical investigation for the treatment of solid tumors (Laack et al., 2010). And several new generation TKIs have been tested in NSCLC.

Authors like Pallis et al. (2013) and Giaccone et al. (2011) had made a detailedly presentation in this issue, so here, we just briefly mentioned some latest clinical trials.

Afatinib (BIBW 2992), an irreversible and double EGFR and HER-2 TKI, have gone on to demonstrate the efficacy in patients harboring activating EGFR mutations. In a phase IIb/III trial in patients who had progressed after at least 12 weeks of treatment with an EGFR-TKI. This trial failed to demonstrate an OS benefit (HR = 1.08; 95% CI 0.86–1.35)and the P value showed no significant (Miller et al., 2012), though the median PFS was longer in the Afatinib group (3.3 months, 95% CI 2.79–4.40) than it was in the placebo group (1.1 months, 0.95–1.68; HR= 0.38, 95% CI 0.31–0.48; p<0.0001).And in a post hoc analysis of 391 patients who were considered as highly likely to have EGFR mutations (long duration of response to prior treatment with EGFR–TKIs) showed that Afatinib significantly prolonged PFS (4.4 months vs. 1 month for placebo) and showed a trend toward improved OS (Miller et al., 2010), and in the recent report about the symptoms and Health-related quality of life (HRQoL) benfit from this clinical trials had shown that Afatinib significantly improved NSCLC–related symptoms and HRQoL (Hirsh et al., 2013). Neratinib (HKI-272) is another oral, irreversible, EGFR and HER-2 inhibitor and had been tested in a phase II trial in NSCLC patients (Sequist et al., 2010), This phase II trial included patients with prior TKI therapy (both EGFR mutation positive and wild-type) and TKI-naïve patients with adenocarcinoma and light smoking histories (≤20 pack-years). The primary end-point of the study was ORR. But unfortunately the drug was not active in this population (ORR of 3%) and no patient with T790M mutation responded. After the results of this trial, further development of Neratinib in NSCLC was halted (Pallis and Syrigos, 2013) and the reason of this result had not very clear. Dacomitinib (PF-00299804), a new, irreversible, oral TKI of EGFR, HER-2 and HER-4. It has shown encouraging results in Asian patients (Park et al., 2010) and in Caucasians (Campbell et al., 2010) as third line treatment after chemotherapy and TKIs.

Other second generation EGFR-TKIs, like Crizotnib (PF-02341066) had shown a striking outcome vs chemotherapy (pemetrexed or docetaxel) in a phase III trial (Shaw et al., 2013), the median PFS was 7.7 months in the Crizotinib group and 3.0 months in the chemotherapy group (HR=0.49; 95% CI, 0.37 to 0.64; P<0.001). The RR (response rates) were 65% (95% CI, 58 to 72) with Crizotinib, as compared with 20% (95% CI, 14 to 26) with chemotherapy (P<0.001) and Figitumumab (CP-751,871) have the potential to overcome EGFR resistance and are currently being investigated in clinical trials (Goto et al., 2012).

Discussion

The discovery of EGFR-TKIs as an effective mean, both as first and subsequent lines of therapy in the recent decades, ushered in the era of personalized medicine in NSCLC treatment. Instead of cytotoxic chemotherapy, patients with activating EGFR mutations now have the option of taking an oral pill with relatively tolerable side effects and a longer life expectancy (Nguyen and Neal, 2012). However, the overwhelming majority of these patients would eventually develop acquired resistance to either drug and it remains a challenging problem. Based on our compile, we consider that patients who were progressed after benefit from the prior EGFR-TKI, after a drug holiday with systemic chemotherapy and/or chemo-radiotherapy, it is feasible to retrial with the original TKI for there exists evidence that the genetic mechanisms of acquired resistance could be lost in the absence of selective pressure from TKIs (Sequist et al., 2011) and the tumor continue to be "oncogene-addicted" to EGFR (Oh et al., 2012), but the premise is only for those who were benefit from Gefitnib or Erlotinib at an initial course. Our results confirmed that more than half of the patients (55.9%) could benefit from a second course of EGFR-TKI. The outcome of switching between Erlotinib and Gefitinib was unsatisfactory compared with the great enthusiasm invested in this field before. The disease control rate treated with the other TKI after failure of one kind of TKI was 43.2%. It was lower than the restore option but had a relatively large increase compared with Kaira et al's (Kaira et al., 2010) investgation (43.2% vs 29.2%) in 2010. From Table 4 we can see that except one prospective study discussed about switching to Gefitnib after failure of Erlotinib, other reports by our updated were all retrospective trials or case reports and accompanied with the comprehending to "potential benefits population" by physicians in the recent 5 years, these inevitably contributed to the probability of selection bias and the increase did not convert to the survival benefit apparently, statistical analysis also shown that the status of EGFR mutations were not positive predictors for responding after failure of one kind of TKI. We consider that as a salvage option after failure of TKI, the other drug should be carefully considered in a select subset of patients and it is not recommended to convert to the other EGFR-TKI immediately after one kind of TKI resistant. Noteworthily, special attention should be paid for those EGFR mutant NSCLC patients with asymptomatic or local progression especially in CNS, autopsy reports had shown that CNS metastases may remain free of mutations associated with secondary resistance, despite the development of such mutations in systemic sites of disease. This was likely a result of poor drug penetration in the CNS obstructed by the Blood Brain Barrier (BBB) because sites of CNS progression may still have tumors that remain sensitive to treatment with the TKI if adequate concentrations of drug can be delivered into the CNS (Balak et al., 2006; Jackman et al., 2006). Many experts still believe that those patients who experienced oligo-CNS relapse should not be considered as having systemic acquired resistance to EGFR-TKI therapy (Jackman et al., 2010). So continuation of EGFR-TKI as systemic treatment plus local intervention like radiotherapy to control the local progression was rational in clinical practice and recent reports by our summary also support this treatment option, but this proposal still need to be verification by clinical trials. As another effective mean to treat NSCLC, what we are interested in is whether using EGFR-TKI combined with radiotherapy at the initial stage for their mechanisms to kill tumors were completely different and might

translate into clinical benefit for those patients who have limited treatment options at present. Crucially, identify the molecular alterations by rebiopsy that lead to resistance to Erlotinib/Gefitinib (like secondary mutation of the EGFR gene, amplification of the MET gene, HER-2 mutations, etc.) is urgent and would facilitate the development of strategies overcoming resistance and maximizing patients' benefits. A reasonable strategy to overcome acquired resistance to the first-generation EGFR-TKIs seems to use one of the several second-generation TKIs mentioned above, typified by irreversible EGFR-TKIs, Many of these irreversible inhibitors have demonstrated activity in preclinical studies. But it remains to be elucidated for the clinical results of these agents are not very encouraging especially in patients with progression after failure of Erlotinib/Gefitinib. Instead of using signal agent, another option is to use a combination of two targeted drugs that dual block the EGFR signaling pathway. For example the combination of Afatinib with Cetuximab was tested in NSCLC patients after failure of Erlotinib/Gefitinib treatment (Janjigian et al., 2011), the encouraging results of this combination provides a potential therapeutic option for this population. Since NSCLC has several genetic alterations more than just EGFR mutation, trying to block two or more targets also seem to be an optimal approach to substantially improve clinical outcome and this rationale is also being tested in several clinical trials. We predict that good results will finally obtain with researches on the mechanism of resistance deeper and we look forward to reviewing future analyses.

In conclusion, retrospective studies and case reports account for the vast majority of this review, and researchers have used different inclusion/exclusion criteria, especially on the duration of time a patient must be treated with an EGFR-TKI before enrollment and/or the duration of time a patient should be off the EGFR-TKI before starting other therapies. Up to now, there were still no established treatment modes for patients after EGFR-TKI failure and some recommendations are still in low-level evidence. Trials including ASPIRATION (Park et al., 2012), IMPRESS (NCT01544179) and a prospective study conducted by Guangdong General Hospital are ongoing to explore the treatment strategies for EGFR-TKI failure and we still have a long way to overcome the resistance to EGFR-TKI.

Acknowledgements

Study designed by Shixiu Wu. Tao Song and Wei Yu collected data, generated the data base, Tao Song performed the statistical analysis and wrote the manuscript. All authors read and approved the final manuscript.

References

Asahina H, Oizumi S, Inoue A, et al (2010). Phase II study of gefitinib readministration in patients with advanced non-small cell lung cancer and previous response to gefitinib. *Oncology*, **79**, 423-9.

Asami K, Kawahara M, Atagi S, Kawaguchi T and Okishio K (2011). Duration of prior gefitinib treatment predicts survival potential in patients with lung adenocarcinoma receiving subsequent erlotinib. *Lung Cancer*, **73**, 211-6.

Balak MN, Gong Y, Riely GJ, et al (2006). Novel D761Y and common secondary T790M mutations in epidermal growth factor receptor-mutant lung adenocarcinomas with acquired resistance to kinase inhibitors. *Clin Cancer Res*, **12**, 6494-501.

Bean J, Brennan C, Shih JY, et al (2007). MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. *Proc Nat Acad Sci*, **104**, 20932-7.

Becker A, Crombag L, Heideman DA, et al (2011). Retreatment with erlotinib: Regain of TKI sensitivity following a drug holiday for patients with NSCLC who initially responded to EGFR-TKI treatment. *Eur J Cancer*, **47**, 2603-6.

Campbell A, Reckamp K, Camidge D, et al (2010). PF-00299804 (PF299) patient (pt)-reported outcomes (PROs) and efficacy in adenocarcinoma (adeno) and nonadeno non-small cell lung cancer (NSCLC): A phase (P) II trial in advanced NSCLC after failure of chemotherapy (CT) and erlotinib (E). *J Clin Oncol*, **28**, 7596.

Chaft JE, Oxnard GR, Sima CS, et al (2011). Disease flare after tyrosine kinase inhibitor discontinuation in patients with EGFR-mutant lung cancer and acquired resistance to erlotinib or gefitinib: implications for clinical trial design. *Clin Cancer Res*, **17**, 6298-303.

Chang JW, Chou CL, Huang SF, et al (2007). Erlotinib response of EGFR-mutant gefitinib-resistant non-small-cell lung cancer. *Lung Cancer*, **58**, 414-7.

Cho BC, Im CK, Park MS, et al (2007). Phase II study of erlotinib in advanced non-small-cell lung cancer after failure of gefitinib. *J Clin Oncol*, **25**, 2528-33.

Costa DB, Nguyen KS, Cho BC, et al (2008). Effects of erlotinib in EGFR mutated non-small cell lung cancers with resistance to gefitinib. *Clin Cancer Res*, **14**, 7060-7.

Downey RJ, Ng KK, Kris MG, et al (2002). A phase II trial of chemotherapy and surgery for non-small cell lung cancer patients with a synchronous solitary metastasis. *Lung Cancer*, **38**, 193-7.

Faehling M, Eckert R, Kamp T, et al (2013). 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. Lung Cancer, **80**, 306-12.

Fukuoka M, Wu YL, Thongprasert S, et al (2011). Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol*, **29**, 2866-74.

Garfield DH (2005). Modern treatment of lung cancer: case 2. Response to erlotinib after failure of gefitinib in a patient with advanced non-small-cell lung carcinoma. *J Clin Oncol*, **23**, 7738-40.

Giaccone G and Wang Y (2011). Strategies for overcoming resistance to EGFR family tyrosine kinase inhibitors. *Cancer Treat Rev*, **37**, 456-64.

Goto Y, Sekine I, Tanioka M, et al (2012). Figitumumab combined with carboplatin and paclitaxel in treatment-naive Japanese patients with advanced non-small cell lung cancer. *Invest New Drugs*, **30**, 1548-56.

Gridelli C, Maione P, Galetta D, et al (2007). Three cases of long-lasting tumor control with erlotinib after progression with gefitinib in advanced non-small cell lung cancer. *J Thorac Oncol*, **2**, 758-61.

Grossi F, Rijavec E, Dal Bello MG, et al (2012). The

administration of gefitinib in patients with advanced non-small-cell lung cancer after the failure of erlotinib. *Cancer Chemother Pharmacol*, **69**, 1407-12.

Guo R, Chen X, Wang T, et al (2011). Subsequent chemotherapy reverses acquired tyrosine kinase inhibitor resistance and restores response to tyrosine kinase inhibitor in advanced non-small-cell lung cancer. *BMC Cancer*, **11**, 90.

Hanna N, Shepherd FA, Fossella FV, et al (2004). Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol*, **22**, 1589-97.

Hata A, Katakami N, Yoshioka H, et al (2011). Erlotinib after gefitinib failure in relapsed non-small cell lung cancer: clinical benefit with optimal patient selection. *Lung Cancer*, **74**, 268-73.

Hirsh V, Cadranel J, Cong XJ, et al (2013). Symptom and quality of life benefit of afatinib in advanced non-small-cell lung cancer patients previously treated with erlotinib or gefitinib: results of a randomized phase IIb/III trial (LUX-Lung 1). *J Thorac Oncol*, 8, 229-37.

Jackman D, Pao W, Riely GJ, et al (2010). Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. *J Clin Oncol*, **28**, 357-60.

Jackman DM, Holmes AJ, Lindeman N, et al (2006). Response and resistance in a non-small-cell lung cancer patient with an epidermal growth factor receptor mutation and leptomeningeal metastases treated with high-dose gefitinib. *J Clin Oncol*, **24**, 4517-20.

Janjigian Y, Groen H, Horn L, et al (2011). Activity and tolerability of afatinib (BIBW 2992) and cetuximab in NSCLC patients with acquired resistance to erlotinib or gefitinib. *J Clin Oncol*, **29**, abstr7525.

Jensen SB, Pedersen AM, Vissink A, et al (2010). A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: management strategies and economic impact. *Support Care Cancer*, **18**, 1061-79.

Kaira K, Naito T, Takahashi T, et al (2010). Pooled analysis of the reports of erlotinib after failure of gefitinib for non-small cell lung cancer. *Lung Cancer*, **68**, 99-104.

Kim H, Kim Y, Oh S, et al (2008). Response to erlotinib after failure of gefitinib in non-small cell lung cancer with EGFR mutation. *J Clin Oncol*, **26**, 19072.

Koizumi T, Agatsuma T, Ikegami K, et al (2012). Prospective study of gefitinib readministration after chemotherapy in patients with advanced non-small-cell lung cancer who previously responded to gefitinib. *Clin Lung Cancer*, **13**, 458-63.

Kurata T, Tamura K, Kaneda H, et al (2004). Effect of re-treatment with gefitinib ('Iressa', ZD1839) after acquisition of resistance. *Ann Oncol*, **15**, 173-4.

Laack E, Sauter G and Bokemeyer C (2010). Lessons learnt from gefitinib and erlotinib: Key insights into small-molecule EGFR-targeted kinase inhibitors in non-small cell lung cancer. *Lung Cancer*, **69**, 259-64.

Lee DH, Kim SW, Suh C, et al (2008). Phase II study of erlotinib as a salvage treatment for non-small-cell lung cancer patients after failure of gefitinib treatment. *Ann Oncol*, 19, 2039-42.

Li XD, Geng YT, Wu CP, et al (2010). Restoration of gefitinib efficacy following chemotherapy in a patient with metastatic non-small cell lung cancer. *Onkologie*, **33**, 466-9.

Luo D, Huang M, Zhang X, et al (2012). Salvage treatment with erlotinib after gefitinib failure in advanced non-small-cell lung cancer patients with poor performance status: A matched-pair case–control study. *Thoracic Cancer*, **3**, 27-33.

Marquez-Medina D, Chachoua A, Martin-Marco A, et al (2013). Continued erlotinib maintenance and salvage radiation for solitary areas of disease progression: a useful strategy in selected non-small cell lung cancers? *Clin Transl Oncol*.

Miller V, Hirsh V and Cadranal J (2010). Subgroup analysis of LUX-Lung 1: a randomized phase III trial of afatinib (BIBW 2992)+ best supportive care (BSC) versus placebo+ BSC in patients failing 1–2 lines of chemotherapy and erlotinib or gefitinib [abstract LBPL3]. *J Thorac Oncol*, **5**, S557.

Miller VA, Hirsh V, Cadranel J, et al (2012). Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol*, **13**, 528-38.

Nguyen KS and Neal JW (2012). First-line treatment of EGFR-mutant non-small-cell lung cancer: the role of erlotinib and other tyrosine kinase inhibitors. *Biologics*, **6**, 337-45.

Oh IJ, Ban HJ, Kim KS and Kim YC (2012). Retreatment of gefitinib in patients with non-small-cell lung cancer who previously controlled to gefitinib: a single-arm, open-label, phase II study. *Lung Cancer*, **77**, 121-7.

Ohsaki Y, Tanno S, Fujita Y, et al (2000). Epidermal growth factor receptor expression correlates with poor prognosis in non-small cell lung cancer patients with p53 overexpression. *Oncol Rep*, **7**, 603-7.

Pallis AG and Syrigos KN (2013). Epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of NSCLC. *Lung Cancer*, **80**, 120-30.

Park K, Heo D, Cho B, et al, 2010. PF-00299804 (PF299) in Asian patients (pts) with non-small cell lung cancer (NSCLC) refractory to chemotherapy (CT) and erlotinib (E) or gefitinib (G): A phase (P) I/II study, *J Clin Oncol (Meeting Abstracts)*, pp. 7599.

Park K, Tsai CM, Ahn MJ, et al (2012). ASPIRATION: Phase II study of continued erlotinib beyond RECIST progression in Asian patients (pts) with epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC), JOURNAL OF CLINICAL ONCOLOGY. AMER SOC CLINICAL ONCOLOGY 2318 MILL ROAD, STE **800**, ALEXANDRIA, VA 22314 USA.

Pfannschmidt J, Schlolaut B, Muley T, Hoffmann H and Dienemann H (2005). Adrenalectomy for solitary adrenal metastases from non-small cell lung cancer. *Lung Cancer*, **49**, 203-7.

Riely GJ, Kris MG, Zhao B, et al (2007). Prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus. *Clin Cancer Res*, **13**, 5150-5.

Rosell R, Gervais R, Vergnenegre A, et al (2011). Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: Interim results of the European Erlotinib Versus Chemotherapy (EURTAC) phase III randomized trial. *J Clin Oncol*, **29**, 7503.

Saito H, Murakami S, Kondo T, et al (2012). Effectiveness of erlotinib in advanced non-small cell lung cancer in cases of gefitinib resistance after treatment of more than 6 months. *Onkologie*, **35**, 18-22.

Schiller JH, Harrington D, Belani CP, et al (2002). Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*, **346**, 92-8.

Sequist LV, Bell DW, Lynch TJ and Haber DA (2007). Molecular predictors of response to epidermal growth factor receptor antagonists in non-small-cell lung cancer. *J Clin Oncol*, **25**, 587-95.

Sequist LV, Besse B, Lynch TJ, et al (2010). Neratinib, an irreversible pan-ErbB receptor tyrosine kinase inhibitor: results of a phase II trial in patients with advanced non-small-

cell lung cancer. *J Clin Oncol*, **28**, 3076-83.
Sequist LV, Martins RG, Spigel D, et al (2008). First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations. *J Clin Oncol*, **26**, 2442-9.
Sequist LV, Waltman BA, Dias-Santagata D, et al (2011). Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med*, **3**, 75ra26.
Shaw AT, Kim DW, Nakagawa K, et al (2013). Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*.
Shih YN, Liou JL, Jiang WC, et al (2007). Phase II study of erlotinib in patients with advanced non-small cell lung cancer who failed prior gefitinib treatment: P3-150. *Journal of Thoracic Oncology*, **2**, S743.
Shoji F, Kawano D, Ito K, et al (2011). Effectiveness of erlotinib against recurrent pulmonary adenocarcinoma unresponsive to gefitinib: report of a case. *Surg Today*, **41**, 255-7.
Shukuya T, Takahashi T, Naito T, et al (2011). Continuous EGFR-TKI administration following radiotherapy for non-small cell lung cancer patients with isolated CNS failure. *Lung Cancer*, **74**, 457-61.
Sim SH, Han SW, Oh DY, et al (2009). Erlotinib after Gefitinib failure in female never-smoker Asian patients with pulmonary adenocarcinoma. *Lung Cancer*, **65**, 204-7.
Song ZB, Yu YF, Chen ZW and Lu S (2011). Erlotinib as a salvage treatment for patients with advanced non-small cell lung cancer after failure of gefitinib treatment. *Chin Med J (Engl)*, **124**, 2279-83.
Tomizawa Y, Fujita Y, Tamura A, et al (2010). Effect of gefitinib re-challenge to initial gefitinib responder with non-small cell lung cancer followed by chemotherapy. *Lung Cancer*, **68**, 269-72.
Vasile E, Tibaldi C, Chella A and Falcone A (2008). Erlotinib after failure of gefitinib in patients with advanced non-small cell lung cancer previously responding to gefitinib. *J Thorac Oncol*, **3**, 912-4.
Viswanathan A, Pillot G and Govindan R (2005). Lack of response to erlotinib after progression on gefitinib in patients with advanced non-small cell lung cancer. *Lung Cancer*, **50**, 417-8.
Volm M, Rittgen W and Drings P (1998). Prognostic value of ERBB-1, VEGF, cyclin A, FOS, JUN and MYC in patients with squamous cell lung carcinomas. *Br J Cancer*, **77**, 663-9.
Voltolini L, Rapicetta C, Luzzi L, et al (2010). Surgical treatment of synchronous multiple lung cancer located in a different lobe or lung: high survival in node-negative subgroup. *Eur J Cardiothorac Surg*, **37**, 1198-204.
Walther JC, Khorshid M, Gaya A and Plowman PN (2006). Cross-over response to erlotinib of brain metastatic disease from bronchial adenocarcinoma after gefitinib failure, and an unusual rash. *Clin Oncol (R Coll Radiol)*, **18**, 637-9.
Watanabe S, Tanaka J, Ota T, et al (2011). Clinical responses to EGFR-tyrosine kinase inhibitor retreatment in non-small cell lung cancer patients who benefited from prior effective gefitinib therapy: a retrospective analysis. *BMC Cancer*, **11**, 1.
Weickhardt AJ, Scheier B, Burke JM, et al (2012). Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. *J Thorac Oncol*, **7**, 1807-14.
Wong AS, Soong R, Seah SB, et al (2008). Evidence for disease control with erlotinib after gefitinib failure in typical gefitinib-sensitive Asian patients with non-small cell lung cancer. *J Thorac Oncol*, **3**, 400-4.
Wong MK, Lo AI, Lam B, et al (2010). Erlotinib as salvage treatment after failure to first-line gefitinib in non-small cell lung cancer. *Cancer Chemother Pharmacol*, **65**, 1023-8.
Yano S, Nakataki E, Ohtsuka S, et al (2005). Retreatment of lung adenocarcinoma patients with gefitinib who had experienced favorable results from their initial treatment with this selective epidermal growth factor receptor inhibitor: a report of three cases. *Oncol Res*, **15**, 107-11.
Yano T, Haro A, Yoshida T, et al (2010). Prognostic impact of local treatment against postoperative oligometastases in non-small cell lung cancer. *J Surg Oncol*, **102**, 852-5.
Yokouchi H, Yamazaki K, Kinoshita I, et al (2007). Clinical benefit of readministration of gefitinib for initial gefitinib-responders with non-small cell lung cancer. *BMC Cancer*, **7**, 51.
Yoshimoto A, Inuzuka K, Kita T, Kawashima A, Kasahara K (2007). Remarkable effect of gefitinib retreatment in a patient with nonsmall cell lung cancer who had a complete response to initial gefitinib. *Am J Med Sci*, **333**, 221-5.
Yu HA, Sima CS, Huang J, et al (2013). Local therapy with continued EGFR tyrosine kinase inhibitor therapy as a treatment strategy in EGFR-mutant advanced lung cancers that have developed acquired resistance to EGFR tyrosine kinase inhibitors. *J Thorac Oncol*, **8**, 346-51.
Zhou C, Wu Y-L, Chen G, et al (2011). Erlotinib versus chemotherapy as first-line treatment for patients with advanced< i> EGFR</i> mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *The lancet oncology*, **12**, 735-742.
Zhou ZT, Xu XH, Wei Q, et al (2009). Erlotinib in advanced non-small-cell lung cancer after gefitinib failure. *Cancer Chemother Pharmacol*, **64**, 1123-7.