Asia–Pacific Journal of Clinical Oncology 2006; **2:** 22–31

REVIEW ARTICLE

Targeting epidermal growth factor receptor in lung cancer: Perspective from the Asia–Pacific region

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Abstract

The epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase of the ErbB family that is frequently overexpressed in non-small cell lung cancer (NSCLC), and has been identified as a novel therapeutic target for lung cancer. The development of small molecule EGFR-tyrosine kinase inhibitors (TKI) such as gefitinib and erlotinib has resulted in paradigm shift in the treatment of advanced NSCLC. The impact of EGFR-TKI in the treatment of NSCLC is even greater in Asia–Pacific region because one of the greatest clinical benefits of EGFR-TKI has been seen in patients of East Asian ethnicity. The discovery of somatic mutations in EGFR-tyrosine kinase domain has so far answered some, but not all, of the questions regarding the clinical response to EGFR-TKI in NSCLC. In addition, other molecular profiles such as KRAS mutations have also been found to play an important role in EGFR targeted therapy. In this article, we review EGFR targeted therapy in NSCLC with the focus on perspective from the Asia–Pacific region.

Key words: epidermal growth factor receptor, erlotinib, gefitinib, mutation, non-small cell lung carcinoma.

INTRODUCTION

Lung cancer has been the most common cancer in the world since 1985. In 2002, 1.35 million of people worldwide were diagnosed with this disease, and 1.18 million died from it, accounting for 17.6% of all cancer death.[1] It is by far the most common cancer in men, with the highest rates in North America and Europe, followed by Australia/New Zealand and East Asia. In East Asia, the incidence of lung cancer is highest in China (42.4 per 100 000), followed by Australia/New Zealand (39.1 per 100 000) and Japan (38.1 per 100 000). Similarly in Taiwan, the incidence of lung cancer, currently secondary to liver cancer, has been rising in the past 10 years. In 2004, lung cancer is the second most common cause of cancer death in men and the most common in women. As the mass vaccination program for hepatitis B (HBV), which has been in place since the early 1980s, has significantly decreased the incidence of HBV-related liver cancer, lung cancer is expected to exceed liver cancer as the leading cause of cancer death in the decades to come.[2]

The incidence and mortality of lung cancer are very much influenced by past exposure of tobacco smoking. Globally, an estimated 85% of lung cancer in men, and 47% of lung cancer in women is related to tobacco smoking. However, in the Asia–Pacific region, the impact of smoking on lung cancer, especially for women, has been less conclusive. For example, in Taiwan, only 9% of women with lung cancer are smokers, in contrast to more than 70% in Western countries.[3] In terms of the histologic types, adenocarcinoma is seen in 42.1% of lung cancer in men and 73.4% in women. Several factors that might contribute to the increase of lung adenocarcinoma in Asian women include cooking styles and the presence of carcinogenes in cooking oil fumes, the NAT2 fast acetylator genotype and cytochrome P4501A1 activity.[4,5] How these factors play a role in the lung carcinogenesis might need to be further

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Accepted for publication 3 January 2006.

defined, but obviously the pathogenesis of lung cancer in these populations could be different from what has been described in Western countries. Therefore, treatment strategies will need to be tailored to the unique pathogenesis in Asia–Pacific region.

In the past, the treatment for advanced lung cancer has been disappointing.[6] However, with the introduction of newer and less toxic agents and improvement of supportive care, treatment with platinum agents in conjunction with either taxane agents, gemcitabine, or vinorelbin has become the standard chemotherapy for advanced lung cancer, reaching an overall survival to approximately 9–10 months.[7] Since the cancer growth requires angiogenesis, strategies targeting molecules critical for angiogenesis have also been devised to improve lung cancer treatment. One of the agents is bevacizumab, a monoclonal antibody against vascular endothelial growth factor, which is crucial for angiogenesis in cancer. Results from Eastern Clinical Oncology Group (Trial E4599) have shown that the inclusion of bevacizumab to platinum-based chemotherapy has significantly improved the overall survival of advanced lung cancer to more than one year.[8,9] At the same time, the identification of epidermal growth factor receptor (EGFR), a receptor tyrosine kinase on the lung cancer biology also prompts the development of another class of agents, so-called tyrosine kinase inhibitors (TKI).[10] Because EGFR is overexpressed in 40–80% of NSCLC, the enthusiasm of using TKI to inhibit EGFR in lung cancer is inspired by the successful use of imatinib mesylate, a TKI against BCR/ABL, the hallmark of chronic myelogenous leukemia (CML). Imatinib has revolutionized the treatment for CML because more than 90% of BCR/ABL(+) CML respond to this agent without significant toxcities.[11–13]

TARGETING EGFR IN LUNG CANCER

Many lung cancers (40–80%), mainly NSCLC, overexpress EGFR, making it an ideal target for novel therapies. Therefore, in the effort to develop more specific and effective treatment, EGFR has been identified as a potential target for lung cancer. The EGFR gene is located in chromosome 7p. EGFR is a 170-kDa receptor tyrosine kinase that dimerizes and then phosphorylates tyrosine residues when specific ligands, such as epidermal growth factor (EGF), are engaged.[14] Phosphorylated tyrosines then serve as binding sites for multiple downstream signal molecules critical for cell survival (e.g. PI3K/Akt) and proliferation (e.g. ras/MAPK) (Fig. 1). The overexpression of EGFR in lung cancer is due to (i) overexpression of EGF through epigenetic mechanisms; (ii) amplification of *EGFR*; or (iii) constitutive activation of EGFR by mutations.[15]

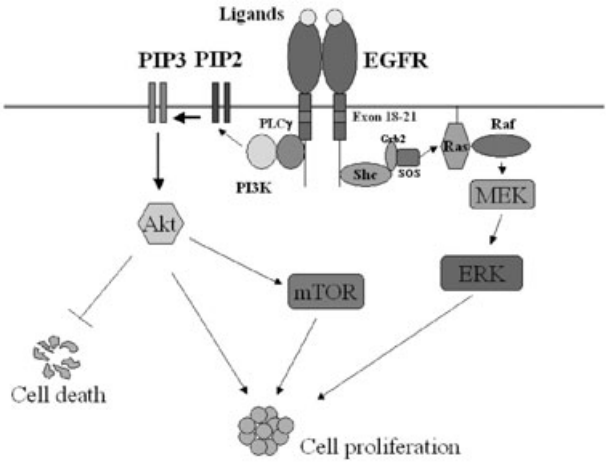

Figure 1 Schematic diagram of epidermal growth factor receptor signaling pathway

USE OF EGFR INHIBITORS IN LUNG CANCER

Since the early 1990s, investigators studying EGFR in carcinogenesis have been trying to identify compounds that can inhibit its catalytic activity. They found an anilinoquinazoline compound that inhibited tyrosine kinase activity. However, *in vivo* studies using this compound showed that it was rapidly metabolized and required constant dosing, which would be inconvenient in the clinic. Later, a modified compound gefitinib (previously called ZD1839; AstraZeneca) was developed with improved stability and better efficacy, and showed high and sustained blood levels in mice over a 24- h period.[16] Gefitinib in a concentration of 5.7 μmol/L after an oral dose of 200 mg/kg in mice competitively inhibits the binding of ATP to EGFR, blocking EGFR's tyrosine kinase activity.[16] The selectivity of gefitinib has been demonstrated using different tyrosine kinases. The concentration required to inhibit the vascular growth factor receptor-KDR or Flt1 is 100 times higher than that needed to inhibit EGFR.[17] Gefitinib does not inhibit other types of kinases, such as serine/threonine kinases, including Raf, MAPK, and MEK1.

Gefitinib has shown great promise in lung cancer in animal studies. In human xenograft tumor models in nude mice, gefitinib alone was given 5 days per week for

2 successive weeks. At doses of 100 or 150 mg/kg, gefitinib can induce partial regressions of xenograft lung cancers.[18] When gefitinib was coadministered with cytotoxic chemotherapy agents or radiotherapy, additive or even synergistic antitumor activity was achieved in xenograft lung tumors in nude mice.[19,20] After the promising activity of gefitinib in NSCLC was seen in phase I studies,[21–23] two randomized, multicenter global and US-based phase II clinical trials were conducted to compare daily oral doses of 250 mg and 500 mg gefitinib as second- or third-line monotherapy in patients with advanced NSCLC.[24,25] The overall response rate in the global Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL)-1 and in the US-based IDEAL-2 was 18% and 10%, respectively. However, the response rate was 28% in Japanese patients in IDEAL-1, significantly higher than 10% observed in non-Japanese patients in IDEAL-1 and 2.[26]

Several preclinical reports have shown that EGFR-TKI can enhance the antitumor activity of chemotherapy, especially when gefitinib was combined with cisplatin, carboplatin, paclitaxel, and docetaxel- the agents commonly used in lung cancer.[27] These results, along with the good tolerability of profile by EGFR-TKI, provide a rationale for the two subsequent randomized phase III trials for previously untreated patients with advanced NSCLC to receive standard platinum-based chemotherapy, with or without the addition of gefitinib at two doses.[28,29] Patients were randomized to receive either gefitinib (250 mg/day or 500 mg/day) or placebo in combination with cisplatin/gemcitabine (INTACT 1, $n = 1093$) or carboplatin/paclitaxel (INTACT 2, $n = 1037$). Disappointingly, both studies failed to show any differences in response rate, time to progression (TTP), or 1-year or overall survival when gefitinib was added. Even though gefitinib was unable to provide significant survival benefit, it was approved in Japan and South Korea in July 2002 for both second- and third-line therapy, and the United States in May 2003 for third-line therapy in advanced NSCLC. Approvals were based on data from the IDEAL 1 and 2 studies, which showed approximately 50% of patients in the IDEAL trials achieved clinical benefit with gefitinib, often associated with symptom relief.[24,25] Thereafter, gefitinib was also approved in many other countries such as Australia, New Zealand, Singapore, and Taiwan. But the use of gefitinib does not come without a price. Although studies in Japanese patients showed higher response rates, they also revealed fatal pulmonary complications.[30] Even so, lung cancer patients, being desperate for a cure, are eager to take on a chance that this novel agent might cure them. Subsequently, a large phase III randomized, placebo-controlled study (ISEL, $n = 1692$) was initiated to evaluate the effect on survival of gefitinib as second- or third-line treatment for patients with locally advanced or metastatic NSCLC.[31] Gefitinib failed to prolong survival in the overall population of patients and those with adenocarcinoma. However, in preplanned subgroup analyses, gefitinib significantly prolonged survival in the never-smokers and patients of Asian origin subgroups.

Erlotinib (Tarceva, previously called OSI774; OSI Pharmaceuticals), another EGFR-TKI, was approved by the US Food and Drug Administration in November 2004 for use in lung cancer. Erlotinib, which has equivalent efficacy to gefitinib in animal studies, is showing results similar to gefitinib. In athymic nude mice xenograft models, erlotinib has antitumor activity both as monotherapy and in combination with chemotherapies.[32,33] In addition, erlotinib also enhances radiation response in xenograft models resulting in profound tumor growth inhibition.[32] In two phase II studies of erlotinib, patient enrollment required EGFR-expressing NSCLC or NSCLC with bronchioloalveolar carcinoma (BAC) histology, respectively.[34,35] The response rate was higher when erlotinib was used as a first-line or second-line therapy in NSCLC with BAC subtype.[35] Erlotinib has also been studied in two large phase III front-line clinical trials in combination with chemotherapy. These two studies randomly assigned patients with good performance status and previously untreated advanced (stage IIIB/IV) NSCLC to erlotinib 150 mg/d or placebo combined with up to a maximum of 6 cycles of carboplatin/paclitaxel (the TRIBUTE study; $n = 1079$) or cisplatin/gemcitabine (TALENT; $n = 1172$) after which patients continued on erlotinib until disease progression.[36,37] The addition of erlotinib to chemotherapy, like what has been found in gefitinib study, did not improve response rate, time to progression, or survival. It is noteworthy that in these two phase III studies the patients enrolled were not selected based on known prognostic factors especially EGFR expression or BAC histologic subtype used in phase II studies. In addition, after retrospective subset analysis of the TRIBUTE study, mutations in EGFR and in KRAS have been found to have important prognostic impact in advanced NSCLC patients treated with chemotherapy with or without erlotinib.[38] The lack of patient selection may have adversely affected the results of these phase III studies. However, in a phase III randomized, placebo-controlled study involving 731 patients, erlotinib as a single-agent therapy can prolong survival in NSCLC

patients who failed first- or second-line chemotherapy.[39] This result will need to be further validated by other studies.

Despite of the promising results in preclinical and early phase studies, anti-EGFR therapy in lung cancer is intriguing in two aspects – the antitumor activity of EGFR inhibitors does not appear to correlate with EGFR expression, and addition of inhibitors to chemotherapy failed to achieve significant additional survival benefit in large randomized controlled trials. This suggests that cancer cells might have evolved multiple pathways for cell proliferation and survival. Simply blocking EGFR signaling is not enough to halt the cancer. Other possible explanations for lack of additional benefit include the possibility that concurrent administration of chemotherapy and EGFR-TKI are antagonistic in at least a subset of patients treated. Preclinical studies have showed that EGFR-TKI result primarily in a G1 cell cycle arrest in cancer cell lines with wild type EGFR, versus induction of apoptosis in cell lines with mutant EGFR.[40] *In vitro* and *in vivo* combination studies have further shown that G1 arrest resulting from pretreatment with EGFR-TKI blocks subsequent effects of chemotherapy, and that continuous concurrent administration of the combination is less effective than intermittent or sequential pulse therapy.[41,42] Clinical studies using alternative ways of combining chemotherapeutic agents with EGFR-TKI in terms of sequences and settings are ongoing.

Currently, there are several small molecule EGFR-TKI under clinical development. These include irreversible EGFR inhibitors (e.g. EKB-569, HKI-272), dual EGF/HER2 receptor inhibitors (e.g. lapatinib and BMS-599626), pan-ErbB receptor inhibitors (e.g. CI-1033), and dual EGF/VEGF receptor inhibitors (e.g. ZD6474).[43–46] Through the inhibition of EGFR and other HER receptors or other TK-receptor families, greater antitumor activity may be achieved and promising clinical result has been reported.[44]

IDENTIFICATION OF *EGFR* MUTATIONS IN LUNG CANCER

Although the clinical trials on gefitinib failed to demonstrate any survival advantage, there are sporadic reports of dramatic response on certain patients. The exact reasons why those patients respond so well remained elusive until the reports in mid-2004 that two groups, using different approaches, first identified the presence of somatic EGFR mutations in NSCLC might correlate with the response to gefitinib.[47,48] In the studies by Lynch *et al.*, they hypothesized that patients with NSCLC who had striking responses to gefitinib had somatic mutations in the EGFR gene that would indicate the essential role of the EGFR signaling pathway in the tumor. They first looked for rearrangements within the extracellular domain of EGFR that are characteristic of gliomas, and none were detected. They then sequenced the entire coding region of EGFR gene in primary lung tumors from patients with a response to gefitinib, from those without a response, and from 25 patients who had never received gefitinib. In another study, Paez *et al.* initially amplified and sequenced the exons encoding the activation loops of 47 of the 58 human receptor tyrosine kinase genes from genomic DNA from a subset of 58 NSCLC samples. Only three of the lung adenocarcinomas showed the same heterozygous somatic missense mutations in *EGFR*. Subsequently, they amplified and sequenced exons 2 through 25 of EGFR in 119 primary NSCLC specimens from patients who had never received gefitinib. Both groups each identified two classes of somatic mutations within the *EGFR* tyrosine kinase domain of their NSCLC specimens that correlate with clinical response to gefitinib. The first class included missense mutations with amino acid substitutions in exon 18 (the p-loop of the kinase domain) or in exon 21 (the activation loop of the kinase domain). The second class involved in-frame deletions within exon 19 that change the structure and spatial orientation of the catalytically important αC-helix of the kinase domain. *In vitro* functional assays in transient transfected Cos-7 cells and lung cancer cell lines showed that these mutant EGFR proteins have enhanced EGF-dependent activation and markedly increased sensitivity to gefitinib inhibition.[47,48]

Several subsequent NSCLC studies have identified more than 29 EGFR mutations among different ethnic groups.[49–58] These mutations are thought to be somatic in origin and most of them are clustered in exon 18–21. They consist of three very different types: in-frame deletions, insertion, and missense point mutations, and are often located in key structural positions in EGFR including the P-loop, the αC-helix, and the A-loop. In-frame deletions in exon 19, accounting for 44% of all mutations, are the most common type of mutations, followed by the missense mutations, a single nucleotide substitution L858R, at exon 21 (41% of all mutations), in-frame insertion at exon 21 (5% of all mutations) and point mutations at exon 18 (4% of all mutations). It is noteworthy that many exon 19 deletions lack amino acids LREA (leucine, arginine, glutamic acid, and alanine) at codons 747 through 750.[47,49] Interestingly, de

novo double *EGFR* mutations were also found in a few of patients.[49,50,58] Studies on the two most common types of mutations have shown that these mutations preferentially activates antiapoptotic pathways (PI3K/Akt and Jak/Stat), but have less effect on cellular proliferation.[59] How lung cancer cells acquire these mutations is still unclear, but it appears to be an early event during carcinogenesis because the presence of mutations does not correlate with disease stage. If this is true, these mutations might arise at the levels of lung progenitor or even stem cells in the airways, making these lung cancer cells ideal targets for EGFR-TKI therapy.

In the initial studies, patients with a dramatic response to gefitinib showed similar profiles: women, patients with BAC or adenocarcinoma, and non-smokers.[24,25] Comparing the mutations rates among different ethnic groups, it is interesting to note that patients with East Asian ethnic background have significantly higher rates of mutations than their Western counterparts (Table 1). In Western countries, the rates of mutations are at most 14% in USA, 7% in Australia, and 4.5% in Italy; while in Asian countries, the mutation rates are significantly higher and could be as higher as 49% in adenocarcinoma. In our series in Taiwan,[58] high frequency of EGFR mutations are found in lung adenocarcinomas, and correlated significantly with female sex, BAC histologic subtype, and non-smokers (Table 2). A similar trend is also observed in Japanese studies. In China, there is female and adenocarcinoma histology preponderance in lung cancer, but there is no significant difference in EGFR mutations between smokers and non-smokers. The profile of patients with EGFR mutations in Korea is similar to that in China. Whether these differences in characterizing mutation-positive NSCLC are caused by variations in sampling, race, or other unidentified factors requires further investigation.

SIGNIFICANCE OF *EGFR* MUTATIONS IN LUNG CANCER PATIENTS IN THE ASIA–PACIFIC REGION

The high mutation rates in the Asia–Pacific region raise several interesting and critical issues. For cancer biology, the high mutation rates in Asian patients imply a different biological process during cancer development. The likelihood that EGFR mutations arise at the level of pulmonary epithelial progenitors and the concept of targeting cancer stem cells, which have also been identified in lung cancer, suggest that a different strategy might be needed for treating these patients.[60] A recent finding that lung cancer with BAC subtype responds more favorably to conventional therapy than with other pathological types suggests that this group of patient will need a separate treatment strategy.[61] Currently, treatment of lung cancer is based on the pathology (small cells *vs* non-small cells), stage of the disease, age, and performance status of patients, but not on tumor biology. Studies on lymphoma, leukemia, breast cancer and gastrointestinal stromal tumors have shown that tumor biology greatly affects the treatment outcome. As with breast cancer, the expression pattern of selected genes has been shown to predict the likelihood of distant recurrence and the survival.[62] Thus, with the new information about EGFR mutations, particularly in the Asia–Pacific region, it may be time to correlate tumor biology with the clinical behavior of lung cancer, to identify new risk factors, and to tailor treatment strategies according to changes at the molecular levels.

The latest information about EGFR mutations appears to be leading us to this direction.[63] Patients with EGFR mutations are more responsive to EGFR-TKI (25 *vs* 9.1% in patients without mutations), and those with deletion at exon 19 appear to respond more favorably than those with exon 21 point mutation. Most important of all, with gefitinib therapy, patients with EGFR mutations have significantly longer survival than those without.[52,54] With the relationship between BAC and EGFR mutations, it requires further studies to understand whether patients with EGFR mutations do survive longer by EGFR inhibitors or if they are inherently more responsive to therapy, regardless whether it is by EGFR inhibitors or by conventional chemotherapy, and whether a combination of EGFR inhibitors and chemotherapy could provide a better control of the disease. Just as small-cell lung cancer has been separated from other types of lung cancer and requires different treatment strategies, it might be time to substratify patients with non-small cell lung cancer, not only by conventional classification, but also by the new genetic information.

If the latest information on the treatment outcomes of EGFR inhibitors is to be considered in the future, should we routinely screen for EGFR mutations in Asia–Pacific region, and how should these mutations be screened? Most investigators currently rely on direct sequencing to detect mutations, and real-time PCR to quantify gene amplifications; these methodologies are technically more demanding than the conventional pathological examination and can only be performed in selected centers. Furthermore, improvement of the detection method will be necessary before it is widely

Table 1 *EGFR* mutations in different ethnic groups

Country	Total no. of patients	No. with mutation (%)	Sex	No. with mutation/total (%)	*p*	Smoking status	No. with mutation/total (%)	*p*	Histologic subtype	No. with mutation/total (%)	*p*
Taiwan (Hsieh),[58]	35	17 (48)	M	4/17 (23)	0.004	Never smoker	14/21 (66)	0.009	Adenocarcinoma	3/14 (21)	0.009
			F	13/18 (72)		Smoker	3/14 (21)		BAC*	14/21 (66)	
Taiwan (Huang),[50]	101	39 (38.6)	M	18/56 (32)	NR	Never smoker	NR	NR	Adenocarcinoma	38/69 (55)	NR
			F	21/45 (46.6)		Smoker			Other	1/32 (3)	
China (Wu),[73]	135	26 (19.3)	M	NR/94	NS	Never smoker	NR	NS	Adenocarcinoma	25/82 (30)	NR
			F	NR/41		Smoker			Other	1/53(2)	
China (Qin),[55]	41	10 (24.4)	M	6/30 (20)	NR	Never smoker	6/21 (28.6)	NR	Adenocarcinoma	7/17 (41.2)	NR
			F	4/11 (36.4)		Smoker	4/20 (20)		Other	3/24 (12.5)	
Japan (Kosaka),[49]	277	111 (40)	M	41/159 (26)	<0.001	Never smoker	76/115 (66)	<0.001	Adenocarcinoma	110/224 (49)	<0.001
			F	70/118 (59)		Smoker	35/162 (22)		Other	1/53 (2)	
Korea (Han),[52]	90	17 (18.9)	M	5/54 (9.3)	0.004	Never smoker	11/43 (25.6)	0.12	Adenocarcinoma	14/65 (21.5)	0.38
			F	12/36 (33.3)		Smoker	6/47 (12.8)		Other	3/25 (12)	
Italy (Marchetti),[51]	860	39 (4.5)	M	18/748 (2.4)	NR	Never smoker	23/115 (20)	NR	Adenocarcinoma	39/375 (10)	NR
			F	21/112 (19)		Smoker	16/745 (2)		Other	0/485 (0)	
USA (Shigematsu),[56]	80	11 (14)	M	3/43 (7)	0.116	Never smoker	7/26 (27)	0.043	Adenocarcinoma	11/44 (25)	<0.001
			F	8/37 (22)		Smoker	4/54 (7)		Other	0/36 (0)	
Australia (Shigematsu),[56]	83	6 (7)	M	1/58 (2)	0.013	Never smoker	4/7 (57)	<0.001	Adenocarcinoma	5/36 (14)	0.081
			F	5/25 (20)		Smoker	2/76 (3)		Other	1/47 (2)	

BAC, bronchioloalveolar carcinoma; F, female; M, male; NR, not reported; NS, not significant. * Includes adenocarcinoma with any bronchioloalveolar features.

Table 2 The relationship of *EGFR* mutations with BAC subtype

Country	No. of adenocarcinoma	No. of ADC	No. of EGFR mutations (%)	No. of PBAC	No. of EGFR mutations (%)	No. of AWBF	No. of EGFR mutations (%)	*p**
Taiwan (Hsieh),[58]	35	14	3 (21)	13	7 (53)	21	14 (66)*	0.009
Taiwan (Huang),[50]	69	66	38 (57)	3	0 (0)	NA	NA	NA
Korea (Han),[52]	65	55	11 (20)	3	1 (33)	10	3 (30)*	0.44
Japan (Kosaka),[49]	224	219	107 (48)	5	3 (60)	NA	NA	NA
Italy (Marchetti),[51]	375	289	17 (6)	86	22 (26)*	NA	NA	0.000002
United States (Shigematsu),[56]	97	80	11 (13)	7	0 (0)	17	4 (27)	NA
United States (Lynch),[47]	22	7	0 (0)	NA	NA	15	2 (13)	NA

ADC, adenocarcinoma other than bronchioloalveolar carcinoma; AWBF, adenocarcinoma with any bronchiolealveolar features including pure bronchioloalveolar carcinomas; BAC, bronchioloalveolar carcinoma; NA, not assessed; PBAC, pure bronchioloalveolar carcinoma. *Compare with adenocarcinoma other than bronchioloalveolar carcinoma.

available to clinical practice. As about 95% of mutations are clustered in four different exons, it is likely to develop rapid and cost-effective methods to screen out mutations before treatment.[64–66]

CLONAL SELECTION AND DRUG RESISTANCE: A DESTINED SCENARIO?

Despite the excitement caused by the dramatic response in patients with EGFR mutations, EGFR-TKI do not provide a cure. Most patients with a good initial response eventually relapse. Studies on CML have demonstrated that cancer cells, which are initially sensitive to imatinib develop resistance by acquiring new mutations or gene amplification.[67] A similar scenario has also been found in gefitinib-resistant lung cancer, in which a second mutation at T790M suppresses inhibition by EGFR inhibitor.[68,69] Although the T790M mutation contributes to the resistance in some cases, the underlying mechanisms for resistance in cases lacking the second mutations remain unclear. A recent report using gene expression profiling has identified epithelial membrane protein-1 (EMP-1), as a potential marker for the resistance of EGFR inhibitor.[70] It is likely that the up-regulation of EMP-1 is caused by drug selection, and that the expression of EMP-1 provides a survival advantage in de novo resistant cases. As EMP-1 is a junctional protein between intracellular microfilaments, and extracellular matrix, it also highlights the importance of tumor microenvironment on drug resistance. Another molecular mechanism that correlates with primary resistance of lung adenocarcinomas to EGFR-TKI is KRAS mutations.[71] Studies on lung cancer resistant to EGFR-TKI have shown that mutations in EGFR and KRAS appear to be mutually exclusive. As RAS is also associated with cell adhesion molecules and intracellular actins, its mechanisms with regard to the resistance to EGFR-TKI might also be related to interaction with tumor microenvironment as well.

How can we overcome the resistance to EGFR inhibitors? Two studies have tried to identify novel compounds to block the EGFR signaling in lung cancer harboring T790M mutations.[46,72] Whether these new compounds could be effective for those resistant lung cancers without T790M mutation is still unclear.

CONCLUSIONS

The story of EGFR mutations so far answers some, but not all, of the questions in lung cancer. In fact, it creates more questions than answers, especially in the Asia–Pacific region. The question of why patients in this region have higher rates of EGFR mutation needs to be further elucidated, both because of its therapeutic relevant to EGFR-TKI and its potentially critical role in the carcinogenesis of lung cancer. Although EGFR-TKI have been shown to increase survival in advanced NSCLC, the magnitude of benefits is different in distinct patient populations. The greatest clinical benefits of EGFR-TKI have been seen in female patients of East Asia ethnicity, who have never smoked and have adenocarcinoma including adenocarcinoma with BAC features. Thus, it is important that pathologists can routinely report the presence or absence of BAC fea-

tures in cases of adenocarcinoma. In addition, NSCLC with unusual clinical manifestations such as those presented with brain metastases, malignant pericardial effusions, or widespread metastases, may also benefit from EGFR-TKI therapy (clinical observations). It is noteworthy that all of these clinical features are associated with EGFR mutations in NSCLC, and EGFR mutation testing in these selected cases may provide important information related to EGFR-TKI therapy. It is also important to establish a standardization of EGFR mutation testing methodology among all the laboratories involved. While EGFR targeted therapy has shifted the paradigm of treatment in lung cancer, a meta-analysis of current studies is still necessary to further clarify its roles. In addition, the development of a decision tree is also needed to indicate criteria under which EGFR-TKI, including its front-line use, is indicated. All of these advancements can only be achieved through concerted efforts among basic researchers, clinical investigators and epidemiologists throughout the Asia–Pacific region.

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