Abstract

Human cancers usually evolve through multistep processes. These processes are driven by the accumulation of abundant genetic and epigenetic abnormalities. However, some lung cancers depend on a single activated oncogene by somatic mutation, termed ‘driver oncogenic mutations’, for their proliferation and survival. EGFR (epidermal growth factor receptor) mutations and ALK (anaplastic lymphoma kinase) rearrangement are typical examples of such driver oncogenic mutations found in lung adenocarcinomas. EGFR-tyrosine kinase inhibitors (TKIs) or ALK-TKIs significantly improved treatment outcomes compared with conventional cytotoxic chemotherapy in patients with lung cancers harboring EGFR mutations or ALK rearrangement, respectively. Therefore, treatment strategies for lung cancers have dramatically changed from a ‘general and empiric’ to a ‘personalized and evidence-based’ approach according to the driver oncogenic mutation. Several novel driver oncogenic mutations, which are candidates as novel targets, such as ERBB2, BRAF, ROS1, and RET, have been discovered. Despite these successes, several limitations have arisen. One example is that some lung cancers do not respond to treatments targeting driver oncogenic mutations, as exemplified in KRAS-mutated lung cancers. Another is resistance to molecular-targeted drugs. Such resistance includes de novo resistance and acquired resistance. A number of molecular mechanisms underlying such resistance have been reported. These mechanisms can be roughly divided into three categories: alteration of the targeted oncogenes themselves by secondary mutations or amplification, activation of an alternative oncogenic signaling track, and conversion of cellular characteristics. Overcoming resistance is a current area of urgent clinical research.

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Lung cancer is the leading cause of cancer-related mortality in many developed countries, including the United States and Japan. Platinum-based systemic chemotherapies have been the standard of care for patients with unresectable or recurrent lung cancers; however, their efficacies are limited, with a median survival time of 7.4–8.1 months typically shown in the ECOG 1594 study. This situation, however, has been changing...
from 2004, the year of the discovery of somatic activating mutations in the epidermal growth factor receptor (EGFR) gene in lung cancers. One of the most important features of EGFR-mutated lung cancers is that these cancers depend on aberrantly activated EGFR signaling (oncogene addiction phenomenon [1]) for their proliferation and survival. Therefore EGFR-mutated lung cancers often dramatically respond to EGFR-tyrosine kinase inhibitors (TKIs), such as gefitinib or erlotinib (fig. 1a, b).
Another important feature of EGFR-mutated lung cancers is that they seldom harbor the concomitant KRAS gene mutations, which were discovered in 1982. This mutually exclusionary relationship between EGFR mutations and KRAS mutations is explained by the presumption that both mutations are ‘driver oncogenic mutations’. A driver oncogenic mutation is one (or a few) genetic change(s) that are essential for development, growth or survival of cancer cells; in contrast with passenger mutations that occur by chance because of the genetic instability of cancer cells during accelerated mitoses.

Anaplastic lymphoma kinase (ALK) gene rearrangement was discovered in 2007 as an alternative mechanism of driver oncogene activation. These tumors respond to ALK-TKI such as crizotinib, as in the case of EGFR-TKI. Currently, identification of patients with EGFR or ALK activation by clinical testing and administration of the relevant drugs form the standard of care. The concept of driver oncogenic mutation-based personalized therapies was established in treatment strategies for lung cancers. Several novel driver oncogenic mutations have been discovered as candidates for future molecular targets (fig. 2). However, there are limitations to molecular-targeted therapies. For example, there is difficulty in targeting lung cancers with KRAS mutations, and there is resistance to molecular-targeted therapies. In this chapter, we summarize the current knowledge of the successes and limitations of molecular-targeted therapies in lung cancers.

Successes in Clinical Application of Molecular-Targeted Therapies

EGFR-Mutated Lung Cancers and EGFR-TKIs

EGFR-mutated lung cancers account for ~40% of adenocarcinomas in East-Asians and ~15% in Caucasians. EGFR-mutated lung cancers are more common in patients who have never smoked, a fact that has attracted the interest of lung cancer researchers to investigate biology of lung cancers unrelated to smoking [2].

EGFR mutations usually occur in the first four exons of the tyrosine kinase domain (exons 18–21) and induce ligand-independent activation of EGFR, followed by signaling through downstream proliferative and antiapoptotic pathways. The types of EGFR mutation are important in EGFR-TKI therapy; lung cancers with either of the two most common mutations, exon 19 deletions and L858R point mutation (exon 21) respond very well to first generation EGFR-TKIs, gefitinib and erlotinib, followed by G719X point mutation (exon 18) and L861Q point mutation (exon 21); exon 20 insertion mutation usually indicates intrinsic resistance.

EGFR mutation as a strong predictive biomarker in the treatment of EGFR-TKIs has been reported in several retrospective analyses, and finally confirmed in biomarker analyses of IPASS (Iressa Pan-Asian Study) [3]. For chemotherapy-naïve patients with EGFR-mutated lung cancers, 6 phase III trials were all able to show that progression-free survival (PFS) of patients treated by EGFR-TKIs (gefitinib, erlotinib, or afa-
In gefitinib trials, overall survival did not differ between treatment arms, probably because of allowed and frequently encountered patient crossover between treatment arms. Retrospective analyses that compared patient survival before gefitinib approval with patient survival after gefitinib approval in Japan clearly indicated that introduction of EGFR-TKI to clinical practice actually doubled the overall survival of patients with EGFR-mutated lung cancers from ~1 year to ~2 years [10].

**Fig. 2.** Identified and potential driver oncogenic mutations in lung cancers. 

- **a** Time course (reported year) of discovery of driver oncogenic mutations is shown. Underlined driver oncogenic mutations indicate a higher prevalence in squamous cell carcinomas, while others do so in adenocarcinomas.

- **b** Prevalence of identified and potential driver oncogenic mutations in lung cancers. Data are combined from some reviews and original researches reporting each driver oncogenic mutation.
Lung Cancers with ALK Rearrangement and Crizotinib

Activation of the ALK gene by forming the EML4-ALK fusion gene through a small inversion within chromosome 2p was discovered in 2007 in lung adenocarcinoma [11, 12]. Because EML4 has a coiled-coil dimerization domain, EML4-ALK is assumed to dimerize without ligand binding and undergo autophosphorylation leading to oncogenic activation. In addition to variants of EML4 segments, other molecules that have a coiled-coil domain are reported to fuse with ALK, including kinesin family member 5B (KIF5B), kinesin light chain 1 (KLC1), or TRK-fused gene (TFG).

ALK-positive lung cancers have distinguishable clinicopathological characteristics. These include a younger age (difference in median age is almost 10 years compared with other types of lung cancers, and some very young patients suffer ALK-positive lung cancers), never smoker or a light smoker status, and acinar, cribriform or signet ring morphology. However, it should be noted that a failure to present with the above-mentioned clinical characteristics does not rule out the possibility of ALK-rearranged lung cancer; i.e. lung cancer in an 80-year-old smoker patient may harbor ALK fusion. ALK fusion has also been identified in lung squamous cell carcinoma at haphazard [13]; however, ALK testing in this histology is not routinely recommended in the National Comprehensive Cancer Network guideline (version 3, 2012) due to its scarcity.

Lung cancers with ALK rearrangement account for 5–7% of adenocarcinomas. Despite such scarcity, development of the ALK inhibitor crizotinib went very smoothly. A high objective response rate (60.8%, 95% CI: 52.3–68.9) and long median PFS (9.7 months, 95% CI: 7.7–12.8) were obtained in phase I study [14]. This resulted in rapid