Editorial

The effect of smoking and *TP53* mutations on molecular-targeted therapy in lung adenocarcinoma patients

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The treatment of non-small cell lung cancer (NSCLC) reached a major turning point with the discovery of gefitinib as an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) and the identification of *EGFR* mutations in 2004 (1). Furthermore, the concept of individualized therapy (precision medicine) has become realistic, as therapeutic target oncogenic driver gene arrangements, such as anaplastic lymphoma kinase (*ALK*), *ROS1*, and *RET*, have been found, and targeted therapeutic drugs have developed (2-4). Developments in genetic analyses using next-generation sequencing and large databases of lung cancer patients have also facilitated the advent of precision medicine (5).

However, not all lung cancer patients benefit from molecular-targeted therapy (6,7), and the development of resistance to drugs that were initially effective remains a serious problem (8-10). A number of issues, such as obtaining detailed patient background information, performing gene mutation analyses, and clarifying the correlations among gene mutations, remain to be managed before true individualized therapy can be implemented. It is necessary to clarify the interaction between frequently occurring gene mutations and the influence of these on drug sensitivity or the prognosis.

The race and life history of patients are certain to be important factors to consider when predicting oncogenic gene mutations. When considering drug therapy for lung cancer patients, the smoking status should always be noted, as smoking is a major risk factor for lung cancer, and the carcinogenic mechanisms of smokers are believed to differ from those of never-smokers (5,11,12). *EGFR* mutations are known to be more frequent in women, adenocarcinoma patients, never-smokers, and Asians (7,13). Although lung adenocarcinoma patients who are eligible for molecular-targeted therapy tend to be non-smokers, it should be noted that some former or current smokers have genetic alterations that make them suitable candidates for molecular-targeted therapeutic drugs, as *ALK* translocation has been found in smoker patients (2). Indeed, approximately 10% of lung adenocarcinoma patients with a smoking history have oncogenic driver mutations (12,13), and the therapeutic response to molecular-targeted therapeutic agents is expected to be good when appropriate molecular-targeted drugs are used. In studies of adenocarcinoma patients with *EGFR* mutations, approximately 30% were smokers; thus, we should perform genetic testing, including testing for *EGFR* mutations, even for patients with a smoking history (11,14). In addition, it should be noted that even in cases with the same sensitizing mutations as those used to indicate EGFR-TKI therapy, the disease control rate and the period for which EGFR-TKIs are effective differ according to the patient's background. Particularly with regard to the response duration, it has been reported that the cumulative smoking dose (CSD) was indirectly associated with the progression-free survival (PFS) and overall survival (OS) in patients with *EGFR*-mutated

lung adenocarcinoma receiving EGFR-TKIs. Kim *et al.* (11) reported the effect of the CSD on the clinical outcomes, including PFS and OS, in patients with *EGFR*-mutated lung adenocarcinoma receiving EGFR-TKIs. Among the 142 patients, including 91 never-smokers, 12 light smokers (0–10 pack-years), 22 moderate smokers (11–30 pack-years), and 17 heavy smokers (>30 pack-years), the median PFS was significantly worse with an increased CSD, with values of 11.8, 11.0, 7.4, and 3.9 months (P<0.001), respectively, and similar results were obtained for the median OS [33.6, 26.3, 20, and 2.9 months (P<0.001), respectively]. The CSD is therefore an important predictive and prognostic factor in patients with *EGFR*-mutated lung adenocarcinoma. When treating smoker patients with EGFR-TKIs, it is necessary to pay attention to the timing at which the drug is changed.

Another thing to consider when conducting molecular-targeted therapy, is interactions with oncogenic driver mutations and other gene mutations. In particular, we should also check for *TP53* mutations. A loss-of-function of the p53 protein, caused by the mutation of the TP53 tumor suppressor gene leads to alterations in DNA repair, apoptosis cell-cycle control and consequently, to genome instability (15). Although there is no targeted therapy for *TP53* mutations, it is necessary to confirm the influence of *TP53* mutations on the efficacy of targeted therapy for other gene mutations. The frequency of *TP53* mutations was reported to be approximately 40% in lung adenocarcinoma patients. As this frequency is relatively high and *TP53* mutations are reported to influence the prognosis of lung cancer patients and anti-cancer drug resistance (13,14,16,17), *TP53* mutations should be confirmed before selecting the method of treatment and drugs. Furthermore, when considering the effects of a *TP53* mutation on carcinogenesis and treatment, we should bear in mind that among the various *TP53* mutations, there are germline mutations associated with Li-Fraumeni syndrome (LFS) and somatic mutations associated with smoking exposure. In a study of 1,730 French patients with symptoms suggestive of LFS, Bougeard *et al.* (18) reported that it might be appropriate to stratify the clinical management of LFS according to the class of the mutation. Ricordel *et al.* (19) reported on two LFS patients diagnosed with *EGFR*-mutated lung adenocarcinoma treated with EGFR-TKIs, and the response to the EGFR-TKIs seemed to be similar to that in individuals with *EGFR* mutations in the general population. They also reported a case of acquired resistance with a T790M second mutation, and noted that this was the same resistance mechanism as observed in the general population without LFS.

The effect of somatic *TP53* mutations on lung adenocarcinoma with molecular-targeted gene mutations has been investigated by several groups (20,21). Aisner *et al.* (21) reported that a concurrent *TP53* mutation, especially a distractive mutation, was associated with poor survival among lung adenocarcinoma patients with drug-sensitive *EGFR* mutations. They also demonstrated that a concurrent *TP53* mutation was associated with poor survival among lung adenocarcinoma patients with *EGFR*, *ALK*, or *ROS1* alterations. Furthermore, Molina-Vila *et al.* (20) reported that a nondisruptive mutation in the TP53 gene was an independent prognostic factor for reduced survival in cases of advanced NSCLC with *EGFR* wild-type or *EGFR* mutations. Further investigations will be necessary to clarify the interactions between *EGFR* mutations and *TP53* mutations with regard to the prognosis and drug sensitivity of lung adenocarcinoma.

In order to establish individualized therapy and improve the prognosis of lung cancer patients, it is necessary to clarify the interaction between tumor suppressor gene mutations, especially *TP53* mutations, and the mechanism of drug resistance. The smoking status and *TP53* mutation status are associated with the efficacy of not only molecular-targeted drug but also novel immunotherapeutic agents (22). To construct individualized therapeutic regimens and improve the prognosis of lung adenocarcinoma, we must efficiently and accurately identify the oncogenic driver mutations and suppressor gene mutations in each patient. In the field of cancer therapy, immune checkpoint therapy has become widespread as a novel treatment for lung cancer. At present, since there are no drugs that are effective for all patients, research is ongoing to link gene analyses with patient background information. In Japan, the nationwide SCRUM-Japan cancer genome screening project is trying to construct a system that delivers the most effective therapeutic agents to each patient, which can play a key role in the development of multiplex diagnostic products and novel indications for targeted therapy for precision cancer screening and treatments (23).

With the worldwide development of next-generation sequencing and information technology, many genetic mutations can now be retrieved from a small specimen in a relatively short period of time. To facilitate the selection of effective therapeutic agents and improve the prognosis of each lung cancer patient, it is necessary to clarify the influence of the interaction of gene mutations on different

treatment. To achieve ideal individualized therapy for lung cancer patients, it is necessary to clarify the interaction of various environmental factors and gene mutations. Ideally, anyone should be able to easily use the accumulated data and determine the most appropriate treatment for each lung cancer patient.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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