L'Institut Servier Annual Scientific Sessions

19th Colloquium 2019
Revolutions in cancer treatment:
how can they be integrated?

Lung cancers

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Springer Healthcare

Abstract

The approved treatments for advanced-stage lung cancers are chemotherapy, immunotherapy and targeted therapies. The latter have been developed thanks to knowledge of intracellular biological pathways that are essential to the cancer cell, particularly in situations where oncogene addiction is present. In lung cancers, the first pathway for which a targeted therapy was approved is the epidermal growth factor receptor (EGFR) pathway, followed by pathways targeting the ALK, ROS, BRAF, MET and RET receptors. It is recommended that molecular abnormalities are routinely examined so that specific therapies can be targeted and prescribed. If resistance occurs, sequential treatment with second- or third-generation targeted therapies can be prescribed before considering chemotherapy. The newest generation of targeted therapies are sometimes very effective from the start, and clinical trials are being carried out to define the best treatment strategies for patients.

Data released in 2018 show that lung cancers are in third most common cancers in France (in terms of incidence), with approximately 50,000 new cases detected each year. The projected number of deaths from lung cancer is the highest of all, with more than 30,000 cases in 2018. However, the mortality rate in this population has been successfully reduced in the past few years. We now have an increasing understanding of the complex intracellular and intravascular biological pathways involved in lung cancers, which are classified into a number of different circuits (motility, proliferation, differentiation and viability).[1] Targeted therapies have been developed as a result of this improved knowledge of the functioning of the cancer cell and the molecular abnormalities responsible for oncogene addictions. These targeted therapies mainly act at the level of signal transduction, the best known of these is the pathway involving tyrosine kinase receptors. This pathway can be blocked by monoclonal antibodies or enzyme inhibitors. The diagnostic test is carried out for molecular abnormalities; the altered protein is the therapeutic target and the effects on the intracellular and vascular biological pathway are measured by the progression of the disease.

TARGETING ONCOGENE ADDICTION

A cancer cell has a number of molecular abnormalities, but only the abnormalities responsible for oncogene addictions are targeted. These are the ones which, when they are inhibited, allow the cell to differentiate again or die by apoptosis. Targeting oncogene addiction has changed the way in which we present results – in the form of waterfall plots[2, 3] – because the response rates achieved with these therapies are much higher than those achieved with chemotherapy. Forms of treatment that target oncogene addiction have significantly altered survival rates for patients with lung cancer.[4] In the 1980s, the survival rate for patients with lung cancers who were treated with chemotherapies based on platinum salts was 5 to 6 months; in the 2000s, third-generation chemotherapy drugs made it possible to improve their median survival to some extent. Targeted therapies like bevacizumab then appeared and the median survival reached 10–12 months in patients with metastases. With the emergence of the first targeted therapies in 2009, median survival reached 15–20 months. When targeted therapies were offered to patients with mutations in the epidermal growth factor receptor (EGFR) gene, their median survival reached 30 months with second-generation tyrosine kinase inhibitors (TKIs) and then 40 months with third-generation TKIs. Finally, median survival has been extended to 5–7 years in patients with ALK mutations who are treated sequentially with first, second and third generation TKIs.

The Biomarqueurs France (Biomarkers France)[5] study initiated by the French-speaking Thoracic Oncology Intergroup (*Intergroupe Francophone de Cancérologie Thoracique – IFCT*) has made it possible to carry out systematic screening for mutations in the *EGFR* gene, *ALK* rearrangements, and the *HER2* (*ERBB2*), *KRAS*, *BRAF* and *PIK3CA* mutations in patients with advanced non-small cell lung cancer. This study showed the clinical benefit obtained from the detection of genetic alterations, because patients who carried a molecular abnormality had improved survival compared with patients who were not carriers. This improvement in survival mainly affected patients with a mutation in the *EGFR* gene, specifically because it is the most common mutation (11% of patients versus 2% in the case of patients with mutations to the *BRAF* gene and 5% for patients with a mutation of the *ALK* gene),[5] but also because it is not yet possible to target all molecular addictions that are possibly linked to a specific role in carcinogenesis.

The prevalence of mutations varies depending on the patient phenotype. In non-smokers, for example, who represent 12% of patients with lung cancers, 44% have an *EGFR* mutation and 14% have an *ALK* mutation; these rates are 3 to 4 times higher than in the general population. Today, an important part of the work of an oncologist or organ specialist involves making sure that appropriate screening for molecular abnormalities has been performed in order to prescribe the most suitable treatment.

MUTATIONS IN EGFR, ALK, KRAS

In lung cancers, the main molecular abnormality affects the *EGFR* gene, with mutations in the intracellular tyrosine kinase domain. These mutations induce constitutive EGFR activation that is independent of its ligand.[6] The signalling pathways involve PI3K, Akt, and mTOR for cellular survival, and RAS, RAF, MEPK, and ERK for the MAP kinases pathway which influences cell proliferation. Clearly this type of intracellular mutation cannot be sensitive to anti-EGFR monoclonal antibodies, but it does result in sensitivity to first-, second- and third-generation TKIs such as gefitinib, erlotinib, afatinib or osimertinib.

Targeted therapies are effective for a number of months, then mechanisms of resistance appear (such as secondary mutations, changes in phenotype, activation of other cellular pathways).[7] These resistance mechanisms may involve the exon 20 T790M mutation for *EGFR*, *MET* or *HER2* amplifications, or mutations of *EGFR C797S*, *PIK3CA* and *RAS*. In lung cancers, progression-free survival (PFS) on first- and second-generation TKIs is usually ~10 months. For third-generation TKIs, PFS is ~19 months. When progression occurs, it is necessary to re-biopsy the tumour to analyse any new molecular abnormalities. The third-generation TKIs usually not only target the resistance mutation but also the initial mutation; so these are therapies that are very effective from the outset. The question is: should treatment with a third generation TKI be offered initially? Or a sequence of first- or second-generation TKI followed by a third-generation TKI, since that we lose about 30% of patients between two lines of treatment? The FLAURA study showed that a third-generation TKI (osimertinib) given to patients at the outset may make it possible to achieve both longer PFS and longer overall survival, compared with sequential treatment with first- and then third-generation TKIs.[8, 9] Therefore, initiating treatment with a third-generation TKI seems to be a good treatment strategy, and after this the resistance mechanism can be examined to adjust the targeted therapy and achieve several years of survival.

When there are translocations of the *ALK* and *ROS* genes, first-, second- and third-generation TKIs are also used. Examples of which include crizotinib, ceritinib, alectinib, lorlatinib, or brigntinib, which is a particularly effective and well-tolerated TKI. The therapeutic arsenal is robust, with the tools provided by molecular biology and the identification of resistance mutations guiding the choice of the first line of treatment to offer.

Until now, targeted therapies aimed at inhibiting *KRAS* have not been effective in patients with lung cancer. Although there are several types of mutations in *KRAS*, the most common mutation in smokers is *KRAS p. G12C* (found in 13% of men and women with lung cancer) forms when a glycine becomes a valine at position 12. One drug has been developed, AMG 510, which creates a disulfide bond with the cysteine and therefore specifically and irreversibly inhibits *KRASG12C* by keeping it permanently in an inactive state.[10] A phase I study (NCT03600883) carried out in 22 patients recently showed that AMG 510 was effective in terms of response: patients were either stabilised or responders.[11] This is the first time that a treatment based on inhibition of *KRAS* has been effective, admittedly in a small number of patients, but this result is very promising for the population of patients with this *KRAS p. G12C* mutation.

WHICH TREATMENT STRATEGY SHOULD BE USED TODAY?

The approved treatments for advanced-stage lung cancers are chemotherapy, immunotherapy and targeted therapies, but it should be noted that treatment strategy algorithms change every year. Routine examinations should include screening for molecular abnormalities (mutations or rearrangements depending on the relevant gene) to target the oncogene addiction and prescribe approved first-line targeted therapies. Immunohistochemistry study can be used to look for ALK ROS and PD-L1. Pembrolizumab as a PD-L1 immunotherapy and chemotherapies are the other treatment options and reimbursement for the combination of chemotherapy/pembrolizumab is anxiously awaited. In a patient with an addiction and a PD-L1 >50%, it is necessary to be cautious and not prescribe an immunotherapy initially, because immunotherapy as a first line treatment is not a good approach in patients for whom targeted therapies are effective. Often the PD-L1 diagnosis is available before the results of molecular abnormalities; however it is necessary to wait for the molecular biology result because patients with an addiction often express oncogenic PD-L1, so PD-L1 inhibitors will be ineffective.[12, 13]

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