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Personalized chemotherapy of lung cancer: What the radiologist should know

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Abstract Lung cancer is the leading cause of deaths due to cancer in France. More than half of lung cancers are discovered at an advanced-stage. New anticancer treatment strategies (i.e., the so-called personalized or targeted therapy) have recently been introduced and validated for non-small-cell lung cancer (NSCLC), in addition to or in association with standard chemotherapy. Personalized therapy includes tyrosine kinase inhibitors (TKIs), antiangiogenic treatments and immunotherapy. Because these treatments may be responsible for atypical thoracic adverse effects and responses as compared to standard chemotherapy, RECIST 1.1 criteria may be inadequate to evaluate the responses to these agents. The goal of this article was to review personalized treatment strategies for NSCLC, to consider the therapy-specific responses and thoracic complications induced by these new therapeutic agents and finally to discuss future directions for the personalized assessment of tumor response.

Lung cancer is the leading cause of cancer deaths worldwide [1]. Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers and is detected at a late stage in approximately 65% of patients when removal of the tumor by surgery is no longer feasible [2]. The 5-year survival rate of such patients with metastatic lung cancer is lower than 5%, whatever the stage [3].

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Recently introduced treatment options for NSCLC, in addition or in association with standard chemotherapy, are based on a more precise characterization of the lung cancer tissue, both in respect to its histological subtype (squamous-cell carcinoma versus adenocarcinoma) and genotype, via the use of molecular tumor markers and the detection of oncogenic abnormalities [4]. The implementation of ''personalized'' treatments that target tumors of a given biological and genetic profile are therefore subject to prior characterization by pathological and molecular genetics methods [5]. The most compelling example is the treatment of lung adenocarcinomas harboring epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocations with tyrosine kinase inhibitors (TKI). The role of angiogenesis inhibitors and immunotherapy in NSCLC management is also growing. The increased efficiency, measured in terms of progression-free survival and/or overall survival, is encouraging. However, these new treatment strategies may result in responses that are very different from those observed with standard cytotoxic chemotherapy on imaging. Consequently, it has been suggested that the classical RECIST 1.1 criteria [6] used to assess the efficacy of a therapy should be revised.

Radiologists are involved in several stages of the management of patients with suspected or confirmed lung cancer, both before [7] and during treatment. They must be able to adapt to new constraints arising from changes in therapeutic approaches [8]. When the diagnosis is based on the results of histopathological analysis of percutaneous, transthoracic biopsy, the samples collected must comply with the quality requirements needed to meet the new expectations of oncologists in terms of molecular biology and histology [9]. RECIST 1.1 criteria are being increasingly used in the context of post-therapeutic follow-up and interdisciplinary team meetings [10], and should take into account the changes arising from personalized treatment.

The aim of this paper was to review the new targeted therapies for lung cancer and their radiographic responses, including thoracic adverse effects, which radiologists need to be familiar with to correctly interpret computed tomography (CT) images during post-therapeutic follow-up. Finally, we will discuss changes to the assessment criteria used for these new treatment options.

Overview

Polymorphism of lung tumors

The numerous histological subtypes identified for lung cancer reflect variations of the tumor genome ranging from point mutations or the loss or gain of several nucleotides to the deletion or amplification of large chromosomal regions, or even whole chromosomes. Oncogenes are generally enabled by ''activating'' mutations or translocations, or in some cases gene amplification, whereas tumor suppressor genes are silenced by ''inactivating'' mutations, deletions or gene promoter methylation.

Diagnosing molecular abnormalities

In France, the Institut National du Cancer (INCa) has implemented one of the most advanced cancer molecular diagnosis services based on 28 molecular genetics platforms throughout France that diagnose the molecular and genetic abnormalities that can be targeted by specific therapies. This diagnostic service is free and available to all patients treated in France. The Biomarkers France study enables 6 molecular abnormalities to be diagnosed in nearly 20,000 patients with advanced-stage NSCLC per year: *EGFR*, *KRAS*, *HER2* and *BRAF* mutations and *ALK* and *ROS1* gene rearrangements (Fig. 1) [11].

The concept of targeted therapy

The use of a targeted therapy is subject to the tumor having a given molecular mutation; therefore, the patients eligible for each specific treatment represent only a subset of all patients [12]. The concept of targeted therapy can, by extension, be broadened to include all molecules that inhibit tumor growth, such as angiogenesis inhibitors and immunotherapy, even though no predictive markers of the response to angiogenesis inhibitors or immune checkpoint inhibitors have been reported to date.

In practice, two therapeutic classes are currently available and readily identifiable: TKIs (identified by the suffix ''-nib'' on their INN, e.g. gefitinib, erlotinib, afatinib, crizotinib, etc.), and monoclonal antibodies targeting transmembrane proteins (identified by the suffix ''-mab'' on their INN, e.g. cetuximab, bevacizumab, necitumumab or nivolumab) (Table 1) [13].

Tyrosine kinase inhibitors (TKIs)

Mutation of the *EGFR* gene

EGFR mutations are known to ''drive'' certain lung cancers, especially in nonsmokers. The ATP binding pocket of the intracytoplasmic domain of the EGFR receptor exhibits a tyrosine kinase type activity and such mutations result in continuous receptor activation. This in turn activates the proteins of the intracellular signaling pathways involved in tumor cell proliferation, resistance to apoptosis, and cell migration. In patients harboring activating EGFR mutations, tumor cells and all the steps leading to tumorigenesis are literally dependent on the activation of this kinase. The most frequently observed mutations are L858R on exon 21 and the deletion of exon 19. *EGFR* mutations are observed

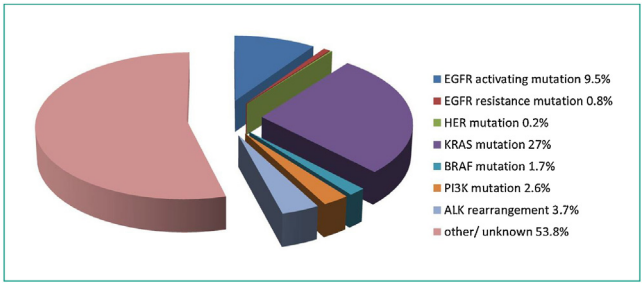

Figure 1. Pie chart showing the genomic subtypes of lung adenocarcinomas based on different driver mutations detected by testing 9911 patients included in the Biomarqueur France cohort (modified from ref. [10]).