Chapter 2

Molecular Therapeutic Approach to the Lung Cancinoma

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Abstract

Long established as a cornerstone of care is lung cancer management that is tailored for age, comorbidities, cancer type, cancer stage, and patient desire. Emerging biologic treatments, immunotherapies, and targeted medicines for non-small-cell lung cancer made possible by advancements in genetics and molecular science are new to this field of personalized management. Based on the distinct molecular properties of a particular patient and the particular malignancy, these techniques have given rise to a new discipline called precision medicine. The most popular care options for stage I through stage III lung cancers continue to be standard management, which includes surgery, chemotherapy, and radiation therapy. Patients with stage IV (i.e., metastatic) lung malignancies stand to benefit the most from advances in precision medicine. The two main components of preoperative evaluation are functional patient assessment and pulmonary function tests. In patients who can withstand surgery, early palliative care and a minimally invasive technique should be taken into account.

INTRODUCTION

Due to the poor prognosis of lung cancer, it is of great importance to detect changes at the molecular level, to increase early diagnosis rates, to improve treatment and to reveal new markers that determine the prognosis in this cancer type. Finding new markers that can distinguish tumor cells from normal cells and identifying individuals who may develop lung cancer are the most important goals today.[1-3] For instance, a recent study found that the overexpression of sLOX-1 and low-density lipoprotein in the serum of NSCLC patients was positively connected and strongly related

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to the TNM stage and metastasis.[3] Serological indicators do, in fact, play a part in cancer screening, diagnosis, treatment response, progression, and recurrence determination, according to numerous research. The biological characteristics of the tumor are thoroughly examined in order to ascertain the molecular makeup of lung cancer, beginning with a study of the protein content of tissues and biological fluids.[1-3] In another study, it was concluded that serum KL-6 levels, which may reflect the molecular length of MUC1, are significantly associated with lung cancer.[2]

The biological systems and cell phenotypes in the organism are controlled by proteins. The proteins that cancer cells release can be used to distinguish them from healthy cells. When other approaches are insufficient, abnormal protein release and cancerous cell proliferation can be detected in the blood at an early stage. The proteomics approach investigates how proteins are secreted from the cell, what role they play within the cell and how they interact with one another, how they alter during cell injury, and the potential role they can play as specific disease markers. For this purpose, many new techniques such as two-dimensional gel electrophoresis, tissue spectrometry, protein array that perform rapid and systemic analysis of thousands of proteins have been developed and used in research.[4] A study using two-dimensional gel electrophoresis identified several proteins that are important for better characterization of tumor development and the molecular specificity of both lung cancer subtypes.[5] They also identified proteins that may be important as biomarkers and/or targets for anticancer therapy.[5] Proteomic tissue samples for early diagnosis of cancer include serum, plasma, tumor tissue samples obtained by surgical and/or bronchoscopic or transthoracic needle aspiration, pleural fluid, urine, sputum and expiratory air analysis.[4,5]

The genomic approach is based on examining the genetic/epigenetic properties of the cell genome at the molecular level, cDNA and oligonucleotides by microarray method. It is used to determine the heterogeneity among histological subtypes of cancer, to investigate the role of genetic alterations in carcinogenesis/DNA repair mechanisms and the role of mutations in cancer predisposition and prognosis of the disease.[6,7] Genomic and proteomic analysis evaluates genes and proteins secreted by cells or tissues with rapid, complementary and parallel analyzes. With genomic or proteomic examinations in cancer tissue, normal tissue or cells are tried to be recognized by determining the different profile of cancer cells. By identifying new molecular targets with gene and protein profiles, it can contribute to treatment failure or prognosis in patient follow-up.[7,8]

Lung Cancer Epidemiology

Lung cancer is the most common type of cancer that causes the most deaths in our country, as it is in the world. Approximately half of patients with lung cancer develop in advanced stages, one quarter develop locally advanced and one quarter develop in early stages. Only 15% of lung cancer cases have a 5 year chance of survival. Up to 90% of lung cancer deaths are related to smoking. Lung cancer is a public health problem because it is common in the community and causes death.[1,9]

According to recent studies, NCLCC groups age, gender, smoking status, co-morbidity index score, clinical TNM stage, pathological stage, tumor location, histological grade, pleural invasion, performance status, clinical stage and causes of death, treatment, stage-specific 5-year significantly different in terms of overall survival rate. Accordingly, these two types have significantly different outcomes in lung cancer. They recommend analyzing these two different cancers separately in order to obtain more precise results in the future.[10]

Etiology and Risk Factors in Lung Cancer

The role of smoking in the development of lung cancer is extremely important and there is a lot of information on this subject. With cigarette smoking, the incidence of lung cancer increases 25-35 times. The increase in the incidence of lung cancer in the last 40 years shows a parallel course with the increase in smoking habits. It is estimated that smoking is responsible for 90% of lung cancer deaths and 30-40% of all cancer deaths. The relationship between smoking and lung cancer varies with dose and duration (dose-response relationship). One out of every 7 people who smoke 2 packs or more a day dies from lung cancer. Due to the presence of metabolites with carcinogenic effects in cigarette smoke, passive inhalation of cigarette smoke at home or at work also increases the risk of lung cancer. The risk of lung cancer increased 1.5 times in passive smokers compared to the normal population. It is estimated that 17% of lung cancers that develop in non-smokers are associated with exposure to cigarette smoke during childhood or adolescence. The risk of developing lung cancer in pipe and cigar smokers is doubled compared to non-smokers. Although smoking is responsible for the development of all types of lung cancer, the strongest association is observed in small cell lung cancer (SCLC) and squamous cell lung cancer.[11,12]

Environmental or occupational carcinogens such as radon, arsenic, asbestos, uranium, nickel are also involved in the etiology of lung cancer. Asbestos used in some workplaces, such as shipyards, increases the risk of

lung cancer. In the case of smoking and asbestos together, the risk increases approximately 29 times. As an environmental carcinogen, asbestos is of little importance. However, it has been determined that natural zeolite fibrils detected in some parts of Central Anatolia in Turkey are responsible for the development of mesothelioma.[13] According to one study, when different categories of tobacco consumption (ie, heavy smokers) are taken into account, lung cancer is associated. This association, albeit to a small extent, has been reported to be similarly increased for people with high indoor radon exposure.[14] Radon is an important carcinogen, especially for miners. It is reported that approximately 25% of lung cancer seen in non-smokers is related to radon. In addition, air pollution and scarring in lung tissue are also known factors in carcinogenesis.[13,14]

Most of the patients are between 50-70 years old. The incidence increases with age. Although it is less likely to occur at younger ages, this incidence is increasing. The age at diagnosis is less than 45 years in 5% of patients.[15]

In parallel with smoking, it is more common in men. However, as a result of the increase in the prevalence of smoking in women in developed countries in our country, the incidence of lung cancer increases more rapidly in women. In addition, histological types also differ between genera. Adenocarcinoma subtype is more common in women.[10,12,15]

Although genetic predisposition in lung cancer is one of the most researched subjects, very reliable findings have not been obtained yet.[14,15]

An association between some systemic diseases such as sarcoidosis, scleroderma and interstitial fibrosis and lung cancer has been reported. The risk of lung cancer is increased threefold in sarcoidosis. On the other hand, the incidence of adenocarcinoma, especially bronchioloalveolar cancer in the lung involvement of scleroderma, is higher than the normal population. In connection with these, the risk of developing cancer in pulmonary scar tissues has increased, despite some controversial comments in recent years. Chronic obstructive pulmonary diseases are also diseases that facilitate the development of cancer.[12,13,15]

Early Diagnosis and Prevention in Lung Cancer

Today, the most effective method for reducing deaths from the disease is the primary prevention approach in the form of reducing cigarette smoking in the community. The only method that has been shown to be effective in lung cancer screening is low-dose lung tomography once a year in high-risk patients. Since the results of years of research have shown that this screening prolongs the survival in heavy smokers, screening programs were started in

the United States of America in 2015 within the scope of "Medicare" and in some European countries.[16]

The results of chemoprevention studies for the high-risk population are inconsistent. Today, an effective preventive agent has not been detected; but work continues.[15,16]

Diagnostic Approach to Lung Cancer

The first examination to be performed in cases with suspected lung cancer due to clinical signs and symptoms is chest X-ray. Radiologically suspicious images of lung cancer are nodular lesions, enlargement of the hilar shadow, rapidly developing nodular infiltrative lesions, non-healing pneumonia, and atelectasis. Histopathological or cytological diagnosis is very important in terms of both the diagnosis of lung cancer and the differentiation of SCLC and NSCLC. Detailed anamnesis and physical examination of the patient are important in terms of both determining the disease sites and detecting lesions that are more accessible for biopsy (such as supraclavicular lymphadenopathy, skin nodules, pleural effusion, hepatomegaly). The easiest method for the diagnosis of the lesion in the lung is sputum cytology. It has a high diagnostic value, especially in central lesions. The diagnostic value of bronchoscopic examination is high (97%). However, this rate may decrease to 55% in peripheral lesions. In this case, the diagnostic intervention that should be attempted in appropriate cases is percutaneous transthoracic needle aspiration. If the diagnosis is still not made after all these interventions, mediastinoscopy or mediastinotomy, thoracoscopy, thoracotomy or, rarely, scalene biopsy can be performed.[17-19]

Staging in Lung Cancer

While TNM staging is used in NSCLC, SCLC is divided into two groups as thoracic-confined disease and extensive disease. TSH defines disease limited to a single hemithorax and regional lymph nodes. In its broadest application, regional lymph nodes consist of ipsilateral hilar, ipsilateral or contralateral mediastinal, and supraclavicular lymph nodes. However, some authors evaluate supraclavicular lymph node metastases.

Histopathology of Lung Cancer

The division of lung cancers into two main groups as SCLC and NSCLC is very important in terms of clinical oncology. Because these two subgroups are very different from each other in terms of both clinical features and biological behaviors and treatment principles. Although the general features

and treatment are similar in NSCLC, there are some differences between the three specific types.[18] The histopathological classification of lung cancers made by the World Health Organization is shown in Table 1. Those in the top four ranks are the most common.

Table 1: Lung cancer classification

NON-SMALL CELL CARCINOMAS

1. Squamous cell carcinoma
2. Adenocarcinoma: a) lepidic b) acinar c) Papillary d) Mucinous
3. Large cell cancer
4. Adenosquamous carcinoma and other mixed tumors

NEUROENDOCRINE TUMORS

1. Carcinoid tumor
2. Atypical carcinoid
3. Small/Large cell carcinoma

Prognostic Factors and Molecular Biological Changes in Lung Cancers

Patient's age, cancer stage, gender (better in females), and patient performance status are prognostic factors that are important in both SCLC and NSCLC. In addition to these, hyponatremia and increase in serum lactic dehydrogenase and alkaline phosphatase levels are also important in SCLC and indicate a poor prognosis.

In recent years, it has become routine to perform pharmacogenetic studies on tumor tissue in patients with metastatic NSCLC. Although it is known that K-ras mutation is a sign of poor prognosis, especially in adenocarcinomas, it has no place in daily practice yet. If the first 2 examinations of tumor tissue have EGFR (Epidermal Growth Factor Gene) mutations (exon 19 del or exon 21 mut) or ALK positivity, it will indicate the use of tyrosine kinase blockers, which can be highly effective in the patient.[3,5,16]

The Role of Molecular Tests and Histopathological Diagnosis in Lung Cancer

In order for the treatment and management of lung cancer to be effective, it is critical to establish a clear histological diagnosis at an early stage. Molecular markers are also one of the key parameters in determining treatment algorithms, especially in adenocarcinomas, and are becoming

increasingly important in squamous cell carcinomas. As of today, it is important to differentiate adenocarcinomas and squamous cell carcinomas from each other in cytological material and small biopsy specimens in advanced disease. This is because in adenocarcinomas, unlike squamous cell carcinomas, pemetrexed or bemecizumab-based chemotherapy protocols have an increased effect on survival independent of progression. In fact, life-threatening hemorrhages have been observed after bevacizumab treatment in patients with squamous cell carcinoma. Finally, detection of EGFR mutations may indicate that the tumor will respond to EGFR tumor kinase inhibitors, which is recommended as first-line therapy in advanced adenocarcinomas.[17,19]

Each institution should adopt a clear and multidisciplinary strategy to patient evaluation, tissue harvesting, tissue processing, and tissue analysis due to the requirement for adequate tissue for histological examination and molecular testing. Adenocarcinoma is typically distinguished from other histological categories by tumor appearance. Studying an immunohistochemical marker for adenocarcinoma and squamous cell carcinoma enables differential diagnosis when a distinct morphology cannot be shown. Lesions with neuroendocrine morphology are identified using neuroendocrine immunohistochemistry markers. All adenocarcinomas should undergo further molecular testing for recognized prognostic and predictive tumor markers (eg, EGFR, KRAS, EML4-ALK fusion gene). The bare minimum tissue and cell block materials needed for decision-making should be used. This emphasizes the value of a diverse strategy. To guarantee that the samples acquired are acceptable for exhibiting morphology and giving enough cell material to allow molecular testing, surgeons, radiologists, and cytopathologists must collaborate.[17,19]

Due to the development of endobronchial and endoscopic ultrasound, electromagnetic navigational bronchoscopy, VATS, and even transthoracic imaging needle biopsies, surgeons are now more involved in the provision of tissue needed for diagnosis in primary, metastatic, and intrathoracic recurrent diseases. A thorough understanding of the crucial subjects is required to receive the proper treatment and the patient's interest.[17,19]

Patient Evaluation for Treatment

The main tumor, metastatic disease, and the patient's functional condition are three crucial areas to consider throughout the therapeutic evaluation (whether the patient will tolerate the appropriate treatment regimen). The surgeon can accurately do clinical staging, evaluate the patient's functional

capacity for therapy, including lung resection, and evaluate the patient systemically by taking a distinct approach to each of these areas.[15,17]

Evaluation of the primary tumor begins with taking a history of symptoms related to pulmonary, nonpulmonary, thoracic, and paraneoplastic syndromes and asking appropriate questions. Since patients are usually presented to surgeons with a chest X-ray or CT images showing the lesion, knowing the location of the lesion can be a guide in guiding the surgeon's anamnesis and physical examination. If the patient does not have a current CT scan of the thorax, it should be taken promptly for the next stage of evaluation. Routine thoracic CT imaging should be performed with intravenous contrast material in order to evaluate the mediastinal lymph nodes adjacent to normal structures in the mediastinum, the primary tumor, and its relationship with the tumor and its surroundings. A thorough understanding and evaluation of CT findings is required to formulate treatment recommendations and to identify options for diagnostic tissue procurement. Suspicion of invasion into adjacent structures is usually based on the history of symptoms, the location of the primary tumor, and CT images. It is common for the primary tumor to be adjacent to the chest wall without clear radiographic evidence of rib destruction. A history of pain in the relevant region is a finding that may indicate involvement of the parietal pleura, ribs or intercostal nerves. Similar observations are also valid for masses adjacent to the recurrent laryngeal nerve, phrenic nerve, diaphragm, vertebrae and thoracic apex. Due to potential evidence of chest wall invasion, thoracotomy shouldn't be skipped since this evidence may call for thoracoscopy or even a thoracotomy. The superiority of MRI over CT for pulmonary lesions and mediastinal nodes has not been shown. Nonetheless, given its dominance in vascular structure imaging, it is a great modality for showing the connections between cancers and vascular structures. This is particularly relevant if using iodinated contrast material is not recommended. For these reasons, MRI is reserved for use in lung cancer patients with contrast allergy, suspected mediastinal, vascular, or vertebral invasions.[1,9,17]

Tissue Diagnostic Options

A surgeon must follow an evidence-based algorithm in his approach to a pulmonary nodule or mass. Depending on the nodule's size, how close it is to the bronchial tree, and the prevalence of cancer in the community under investigation, bronchoscopy has a sensitivity of 20% to 80% in detecting neoplastic processes in pulmonary lesions. Bronchoscopy can be used in the following four ways to obtain diagnostic tissue[1]:

1. Brushing and washing for cytology

2. Direct forceps biopsy from a visible lesion

3. Endobronchial ultrasound-guided fine-needle aspiration biopsy from the invisible but severely compressing lesion

4. Transbronchial forceps biopsy using electromagnetic navigational bronchoscopy or fluoroscopy

Targeted Agents

In NSCLC, a number of genetic changes have been found to promote carcinogenesis. The ERK-MAPK cascade is among the crucial factors in lung cancer that have been described. Lung cancer EGFR, RAS, and BRAF activating mutations cause malignant transformation and alterations in gene expression in this cascade. Tyrosine kinase inhibitors (TKIs) (which account for 25% of instances of adenocarcinoma) are frequently indicative of a lack of effect and are linked to worse overall survival in patients with KRAS-mutant malignancies.[12,13,17,19]

Therapeutic targets are multiplying quickly. Thankfully, toxicity profiles of the medicines being researched for these targets are typically better than those of cytotoxic chemotherapy.[19]

Epidermal Growth Factor Receptor Mutations

Tyrosine kinases are activated by the dimerization of the EGFR cell surface receptor. This process helps to regulate healthy cell growth, angiogenesis, adhesion, motility, and apoptosis. Lack of this control increases a lung cancer cell's ability to become malignant. 15% of lung adenocarcinomas in the US are caused by EGFR mutations, the most prevalent of which are exon 19 (exon 19del) and exon 21 mutations (L858R). Mutations are slightly more likely in women and nonsmokers. In various Asian groups, the prevalence of EGFR mutations rises to 22% to 62% of NSCLCs.[17,19]

The Food and Drug Administration (FDA) has currently approved four EGFR TKIs for use in clinical trials in the United States: erlotinib (Tarceva), gefitinib (Iressa), afatinib (Gilotrif), and osimertinib (Tagrisso). When compared to traditional cytotoxic chemotherapy doublets, this class of drugs has been found to improve progression-free survival (PFS) in patients with advanced NSCLC and activating EGFR mutations. [17,19]

Gefitinib significantly enhanced PFS in the 2009 Iressa Pan-Asia Study trial when compared to carboplatin (Paraplatin) plus paclitaxel (Taxol). In this study, the PFS with gefitinib was doubled, reaching 10.8 months

as opposed to 5.4 months with the doublet of conventional cytotoxic treatment. This study included unselected Asian patients who had a higher frequency of EGFR mutations than people in a Western community. Despite these excellent results and its extensive clinical use in Asia, gefitinib use was restricted in the United States until the FDA approved it in 2015. Gefitinib can be given to patients whose malignancies contain an EGFR exon 19 deletion or an exon 21 L858R mutation. [17,19]

In clinical trials, erlotinib and conventional cytotoxic chemotherapy were also contrasted. Erlotinib shown a striking improvement in PFS of 8 months in the OPTIMAL study when compared to gemcitabine (Gemzar) plus carboplatin. The EURTAC7 and ENSURE8 studies both discovered similar increases in PFS of 5 to 6 months. Despite these gains in PFS, neither of the trials contrasting erlotinib with conventional cytotoxic chemotherapy identified a statistically significant difference in overall survival; this is probably because of crossover of medication after progression.[19]

As an oral, irreversible EGFR and HER2 inhibitor, afatinib. Afatinib significantly improved PFS by 6.7 months in the LUX-Lung 3 study when compared to cisplatin (Platinol) and pemetrexed (Alimta) in patients with EGFR exon 19 deletions and L858R point mutations who had not received therapy before. Afatinib was notable for having 4 treatment-related deaths compared to chemotherapy's zero. Patients with metastatic NSCLC who have tumors with EGFR exon 19 deletions or exon 21 substitution mutations may use afatinib as their first-line treatment, according to FDA approval. With only a 7% response rate, activity is minimal after erlotinib or gefitinib failure. [17,19]

The EGFR T790M mutation in exon 20, which is associated with acquired resistance to TKI therapy, has been found in up to 63% of patients whose illness progresses after an initial response to front-line TKIs. Osimertinib and rociletinib, third-generation EGFR inhibitors, are efficient in preclinical models of EGFR T790M-mutated NSCLC. The objective response rate was between 20% and 30% for patients with T790M-negative illness and around 60% for patients with T790M-positive disease in independent studies of patients whose disease had progressed on EGFR-directed therapy. [17,19]

EML4-ALK Translocations

ALK and Echinoderm Microtubule-Associated Protein-Like 4 (EML4) are translocated because the short arm of chromosome 2 is inverted. This fusion protein, EML4-ALK, activates a number of pathways that promote cell survival and proliferation. These translocations characterize a specific

subset of lung cancer patients and are found in 3% to 5% of NSCLC patients. ALK, MET, and ROS1 kinases are inhibited by the oral medication crizotinib (Xalkori). Crizotinib outperformed cytotoxic chemotherapy in patients with treatment-naive advanced ALK-positive NSCLC in PROFILE 1014, with median PFS of 10.9 months versus 7.0 months, a response rate of 74% versus 45%, and improvements in lung cancer symptoms and quality of life. Because to a 70% crossover rate on progression in the chemotherapy arm, it is likely that there was no statistically meaningful difference in overall survival. Patients who have previously received crizotinib experience a high response rate of 55.4%, and individuals who have never used an ALK inhibitor experience a high response rate of 69.5%. With ceritinib, patients with prior exposure reported a significant 6.9 month PFS. Brigatinib (AP26113) and alectinib (Alecensa), two more ALK inhibitors, have also demonstrated encouraging activity in patients who progressed on crizotinib, including patients with brain metastases. [17,19]

ROS1 Rearrangements

A member of the family of insulin receptors, ROS1 is a tyrosine kinase receptor. ROS1 fuses with at least 12 different partner proteins, resulting in constitutive kinase activity that propels cellular transformation. 1 to 2 percent of NSCLC specimens have ROS1 rearrangements. Those with adenocarcinoma and low or no smoking histories are more likely to have ROS1. In vitro studies and a small number of clinical trials on patients with ROS1 rearrangements have demonstrated that crizotinib can elicit responses. These findings were corroborated by a recent phase I clinical trial, which demonstrated a high response rate of 72% with 6% of patients attaining complete responses. Additionally, all ROS1 fusions demonstrated a benefit, and the median PFS was 19.2 months. [17,19]

BRAF V600 Mutations

Around 2% of lung adenocarcinoma tumors contain BRAF mutations. Vemurafenib (Zelboraf) was administered to 20 patients with NSCLC who had the V600 mutation; this led to a 42% response rate in evaluable patients and a median PFS of 7.3 months. [1,17,19]

MET Amplification or Exon 14 Skipping Mutation

Signal transduction is carried out by the proto-oncogene MET, also known as the hepatocyte growth factor receptor. Exon skipping and MET activation have been proven to be caused by MET exon 14 splice site changes and other mutations, which are found in 2.3% of other lung neoplasms and about

3% of lung adenocarcinomas. These modifications cause the proliferation, invasion, and metastasis of tumor cells. [17,19]

Recommended Testing

Based on these findings, the National Comprehensive Cancer Network's NSCLC guidelines (version 2.2016) advise that as part of comprehensive molecular profiling, all patients with metastatic NSCLC of the histologic subtypes adenocarcinoma, large cell carcinoma, and NSCLC not otherwise specified undergo testing for EGFR mutations and ALK rearrangement. Testing may be considered for patients with squamous cell carcinoma, particularly in never-smokers, mixed histology, or tiny biopsy specimens. The statistics do not now support routine testing of patients receiving curative treatment. All patients, including those with resectable NSCLC, should have routine testing, according to the College of American Pathologists.[15-19]

Immunotherapy

When T cells are activated in response to inflammation or infection in peripheral tissues, they express a protein called PD-1, which is present on cytotoxic T cells and T-regulatory cells. The T cell is rendered inactive upon binding of the PD-1 ligand to its receptor, which suppresses the immunological response to external stimuli. Cancer cells have PD-1 expression, which protects them from immune system attack. By preventing the PD-1 ligand from attaching to its receptor, anti-PD-1 medicines block this pathway, freeing up activated cytotoxic T cells to target the cancer cells. Both non-squamous and squamous cell NSCLCs have shown promise for immunotherapies targeting PD-1 or its ligand, PD-L1.[19]

CONCLUSION

The treatment of advanced lung cancer has lately changed as a result of new medicines. These medicines largely spare normal cells since they target the chemicals causing malignant development. In comparison to traditional cytotoxic chemotherapeutic medicines, targeted treatments and immunotherapies significantly extend patient survival in a subset of patients. Moreover, these medications are frequently more bearable, enhancing life quality and allowing for long-term use. Nevertheless, the advantage has not yet been seen in early illness stages or when used in concert with other modalities.

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