Molecular Targets in Lung Cancer Therapy: A Current Review

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Abstract

Lung cancer presents a heterogeneous nature, which became more and more evident. Generally this type of cancer in an advanced state has a poor prognosis. The discovery of multiple molecular mechanisms, associated to the development, proliferation and prognosis of lung cancer has created new opportunities for a targeted therapy, improving clinical results. Non-small cells lung cancer is characterized by mutations on Epidermal Growth Factor Receptor and/or in the signaling pathways related to this receptor, which promoted the development of selective monoclonal antibodies and Epidermal Growth Factor Receptor-Tirosine Kinase Inhibitors, blocking the proliferation, differentiation, angiogenesis and tumour survival.

Thus, our review highlighted the importance of a continuous research of new molecular targets in lung cancer to achieve better therapeutic outcomes and overall survival rates.

Keywords: Directed therapy; Personalized therapy; Molecular targets and Lung cancer

Introduction

Cancer incidence worldwide has been increasing over the years [1]. Lung cancer (LC) is a disease with a poor prognosis once diagnosed. LC is the leading cause of death in men worldwide and the second cause of mortality in women [2-4]. In Portugal, LC remains as the leading cause of death due cancer in men [5].

LC originates from oncogenic alterations in tissues from the respiratory epithelium, namely in bronchi, bronchioles and alveoli [6]. This cancer results from multiple morphological, molecular and genetic changes, leading to an accumulation of malignant cells [7-9]. LC is mainly classified into two categories, according to its histological characteristics: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is categorized into three different categories, namely adenocarcinoma, squamous cell carcinoma and large cell carcinoma. NSCLC is the most common LC type (about 80% of total cases) and adenocarcinoma is the most common subtype (about 40%). Moreover, bronchioloalveolar carcinoma subtype is more associated with women and non-smokers. In contrast, squamous cell carcinoma is linked to tobacco consumption [2,10-12]. On the other hand, SCLC tends to affect the neuroendocrine system and is related to smoking habit, being diagnosed in only 1% of non-smokers patients [2].

Classification and staging of LC are critical for definitive diagnosis, treatment strategy and to predict the patient’s outcome [2]. Treatment choice depends on a number of factors that are relate to the patient and the tumour, including histology, tumour stage and biology and the general health of the patient [13,14]. LC treatment is based on a set of procedures such as surgery, chemotherapy and radiotherapy [15]. Chemotherapy is widely used in cancer treatment, however, is rarely effective in this type of cancer due to the low amount of drug available in the lung tissue, even if administered in high doses [16].

Recently, it has been investigated a large number of molecular changes such as mutations and gene amplification [17] that could be responsible for tumour survival and directly affect prognosis. Treatments based upon these changes are called targeted or personalized therapies. These treatment protocols aim to target common molecular changes and may increase the survival rate in nonsurgical stages [18,19]. Specific therapy can be used to identify patients at risk for disease, regarding their genomic profile, and provide the appropriate drug with administration of a specific dose at the right time [20]. Thus, there are some mediators which may play a predominant role in the treatment of LC, such as Epidermal Growth Factor Receptor (EGFR), Vascular Endothelial Growth Factor (VEGF), [21], Anaplastic Lymphoma Kinase (ALK), among others [18].

Thus, this study aims to highlight the importance of targeting therapies in lung cancer treatment.

Materials and Methods

This study consists in a review of the literature concerning targeted therapies focused at molecular targets in lung cancer.

The survey of information was carried out in online databases, namely PubMed and Medline database. In this research it was used the keywords: “personalized treatment” and “lung cancer”.

An initial trial of papers of interest was performed by the relevance of the title and content of abstract. Pre-selected articles were completely analysed and properly selected. Selection was performed based on the inclusion criteria: papers in English or Portuguese; review articles or original research papers available in free full text. Exclusion criteria were established as unavailability of selected papers in free full text and papers published before 2005.

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In addition to this, it was also used some information contained in technical books. Finally, all ethical questions have been fulfilled, and all the sources that provided the theoretical support have been properly referenced.

Results

Our survey highlighted the importance of the exploration of specific genetic alterations described in lung cancer cells. Several studies had already described the role of molecular targets such as EGFR and ALK in the development and progression of lung cancer, namely in the cases of NSCLC. However there are other oncogenic alterations in genes that have been identified in NSCLC that we reported in this review as follows, namely VEGF, BRAS, KAS and MET [22].

Epidermal growth factor receptor (Egfr)

EGFR is a transmembrane glycoprotein that plays an important role in carcinogenesis [18]. This receptor is also a critical component of signalling pathway activation, including Ras-Raf-MEK and PI3K-Akt-mTOR pathways [23-25]. EGFR is a member of the tyrosine kinase family and therefore have a response of about 70% to tyrosine kinase inhibitors (TKI) [22].

In NSCLC, EGFR dysregulation has been shown and it could be due to different mechanisms, including overexpression and gene amplification. This receptor has a higher expression in the case of non-smokers and women [26].

EGFR-TKI are a class of drugs well tolerated. However, this class of drugs can induce low to moderate cytotoxic effects at dermatological and gastrointestinal systems [27,28]. Currently, most widely used EGFR-TKI are Gefitinib [29] and Erlotinib. Both are able to inhibiting the catalytic activity of the receptor and thereby inhibiting its auto phosphorylation. This way signal transduction pathway could be inhibited and thus it can induce an anti-tumour effect [18,30]. In a study conducted in Asia and Europe, both drugs showed a very similar activity spectrum, with differences in pharmacokinetics and bioavailability, where Erlotinib showed a higher bioavailability [27].

Another strategy to inhibit the activity of EGFR is the use of monoclonal antibodies, such as cetuximab, panitumumab and others that block ligand binding to the receptor [31]. This type of treatment has been shown to be overexpressed in several tumours in advanced stages. Higher levels of VEGF has been described in squamous cell carcinoma [34]. VEGF family is composed of different proteins denominated VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor (PIGF) [18]. VEGF-A is the most important member, since it is primarily responsible for physiological and pathological mechanisms of angiogenesis. It normally acts by binding to VEGFR-2, causing a signalling cascade. This cascade leads to the activation of transcription factors in the nucleus and, consequently, the formation of new vessels [35].

In tumour cells, this pathway is involved in the induction of tumour cells self-survival and proliferation, as well as formation of new vessels in solid tumours which is essential for the nutrition of tumour cells and its survival [26].

VEGF function can increase mitosis rate of endothelial cells, control vascular permeability and consequently the survival of the vascular endothelium, mechanisms that are activated by the binding of VEGF to its receptors (VEGFR-1, VEGFR-2 and VEGFR-3) [18,26].

VEGF, by its crucial role in carcinogenesis and tumour progression, is an important molecular target for the development of cancer targeted therapies. Bevacizumab is a monoclonal antibody that binds to VEGF-A and is able to neutralize VEGF isoforms. It was observed that treatment with Bevacizumab increases the risk of bleeding, especially into tumours located near the great vessels related to squamous cell carcinoma.

The dual inhibition of EGFR and VEGF is also a treatment option currently used and it could be performed under two strategies. The first one is the combination of specific anti-targeted drugs such as Erlotinib and Bevacizumab, and the second one is the use of an agent with dual activity, Vandetanib, which is a small molecule with anti-VEGF-2, -3 and anti-EGFR activity [18].

Anaplastic lymphoma kinase (Alk)

ALK is a member of tyrosine kinase receptors [36,37], namely insulin superfamily, which is normally expressed in the central nervous system, small intestine and testis [31,38].

EML4-ALK is a fusion protein which results from a short reversal in chromosome 2 and that comprises the intron 13 of EML4 and the intron 19 of ALK, generating an oncogenic fusion encoding a constitutively activated protein [32]. This protein has been found to be overexpressed in some patients with NSCLC. EML4-ALK is able to inhibit apoptosis, thereby favouring proliferation of tumour cells [39]. It is more common in younger patients, non-smokers or smokers with low concentration of accumulated tobacco and adenocarcinoma [18,40]. This translocation is usually linked to unique mutations in EGFR or KRAS and is also associated with resistance to treatment based in EGFR-TKI [31].

Crizotinib was approved for the treatment of patients with mutations in ALK and it was found that it induced a better outcome than common chemotherapy. However, a minority of patients with NSCLC, who had EML4-ALK mutation did not respond to treatment based on Crizotinib which was attributed to mutations related with ALK [41]. Ceritinib (inhibitor of ALK) was approved in April 2014 by the Food and Drug Administration (FDA) for the treatment of patients with NSCLC with resistance to Crizotinib [42].

Some specific inhibitors of BRAF have been approved by the FDA, such as Vemurafenib and Dabrafenib. This drugs act at specific mutations in BRAF-V600E, however only 40 to 50% of patients with BRAF mutation have this specific mutation in BRAF-V600E.
For patients with a mutation in BRAF (V600E-free), are still being developed targeted-therapies [43,44].

**Kras:** Ras proteins or P21 Ras belong to the superfamily guanosine-triphosphate where the three best-known members are KRAS, HRAS and NRAS [10].

KRAS is a GTPase usually located on cell membrane and it is activated by receptors of transmembrane growth factor such as EGFR, HER2, ALK, FGFR and MET [45]. Point mutations in some aminoacids could lead to a compromised GTPase activity. This could result in constitutive activation of downstream signalling cascades. These mutations are found in about 20 to 30% of lung cancer adenocarcinomas [46] and are usually present in conjunction with other mutations in other genes [47].

Usually KRAS is inactivated after GTP to GDP conversion, leading to regulation of cell proliferation and growth. Mutations in KRAS gene result in conversion of GTP to GDP, which induces uncontrolled growth and proliferation of tumour cells [42].

There is currently no effective targeted therapy approved for mutations in the KRAS gene due to loss of normal enzymatic function of Ras [48], which could represent an important area of research in the near future.

**Mesenchymal epithelial transition factor (Met)**

MET is a proto-oncogene located on chromosome 7q21, which encodes a transmembrane receptor tyrosine kinase, the hepatocyte growth factor receptor (HGFR) [31,49]. It can induce inhibition of EGFR protein and then may be a "kinase switch" to ensure cell survival [50].

An increase of MET expression means an acquired resistance to EGFR-TKI and about 20% of patients with resistance to EGFR-TKI treatment had shown an increased amplification of the MET [42,50,51].

There are already some MET inhibitors, such as Cabozatinib that have been approved by FDA for the treatment of specific cancers, but still no clinical evidence on the efficacy of Cabozatinib in patients with NSCLC [42].

**Conclusion**

In the last years, it has been made a significant improvement in the knowledge and perception of biological complexity of the tumour and its microenvironment. This improvement allowed starting a new era of targeted therapy for lung cancer treatment. These new therapeutic strategies based on the identification of specific molecular targets in cancer development and progression mechanisms aims to customize and drive these targets drugs with greater efficacy.

Genetic changes that occur on tumour cells allow oncogenic deregulation of tumour suppressor genes as well as overexpression or activation of genes that promote cancer growth. Structural changes in tyrosine kinase receptors lead to proliferation of tumour cells and thereby creating opportunities for personalized therapy.

Thus, therapy with, for example, EGFR-TKIs and ALK inhibitors, has provided a new treatment for patients diagnosed with lung adenocarcinoma. However, resistance to targeted therapy remains a major obstacle to satisfactory clinical results.

Nowadays, there is a great effort to identify new targets and drugs that can improve the actual therapeutic outcome in which concerns lung cancer treatment. However, this research is still in development, where the great majority of the studies have not yet pass through clinical trials. Most of the targets that are being studied are not fully described and understood, which can lead to the development of several selective drugs for the same molecular target.

Thus, we believe that, in the future, a continuous effort to overcome resistance to targeted therapies already applied in the clinical practice would be of great importance in the advance of LC treatment. Moreover, it is also of crucial importance the continuous study of molecular pathways described as essential for tumour development and progression and the development of new targeted drugs designed to block these pathways.

This research, hopefully, will allow not only a better outcome but also the elimination of severe side effects such those observed in the common chemotherapeutic regimens and a significant increase in quality of life and long-term survival.

**References**


