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Mini Review

A decade of targeted therapy for non-small cell lung cancer

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Abstract

Chemotherapy is one of the main treatment options for cancer. However, chemotherapeutic agents usually suffer from poor pharmaceutical properties that restrict their use. Targeted therapy drugs have been developed to specifically target changes in cancer cells that help these cells to grow. Such drugs often work when standard chemotherapeutic drugs do not, they often have less severe side effects and they are most often used for advanced cancers. The objective of this article is to give an overview about the 16 FDA-approved targeted therapy drugs to treat non-small cell lung cancer.

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. Subtypes of NSCLC include squamous cell carcinoma, adenocarcinoma, large cell carcinoma and the less common adenosquamos carcinoma and sarcomatoid carcinoma.

Many factors increase the risk for NSCLC such as smoking, genetic factors, exposure to radon gas, asbestos, second-hand smoke, or other forms of air pollution.

Signs or symptoms are usually not observed in the early stages of lung cancer, but many signs of eventually developed NSCLC include persistent cough, coughing up blood, persistent breathlessness, unexplained tiredness and weight loss, and an ache or pain when breathing or coughing.

Diagnosis of NSCLC can be achieved with different methods such as chest radiographs and computed tomography (CT) scans, which can be confirmed by biopsy that is usually performed by bronchoscopy or CT-guidance.

Treatment options of NSCLC include surgical tumor removal, radiation therapy, radiofrequency ablation, immunotherapy and chemotherapy. There are a number of factors that determine which methods achieve the best therapeutic outcome. Small tumors are often treated successfully with surgical removal alone because they do not have the potential to metastasize. Malignant tumors, however, are most often treated with a combination therapy. In some cases, non-curative surgery may make other treatments more effective. Chemotherapeutic agents usually suffer from poor pharmaceutical properties such as poor water-solubility or stability, and chemotherapy is accompanied with systemic toxicities. Furthermore, sufficient concentrations of the anticancer drug are often not achieved in tumor cells because of the lack of accumulation of the drugs in solid tumors.

Targeted therapy drugs have been developed to specifically target changes in NSCLC cells that help these cells to grow [1]. Such drugs work differently from the standard chemotherapy, they sometimes work when chemotherapeutic drugs do not, they often have less severe side effects and they are most often used for advanced lung cancers, either as a single therapy or in combination with chemotherapeutic drugs.

Currently, and 11 years after the approval of the first targeted therapy drug Avastin in 2006 [2], 16 FDA-approved targeted therapy drugs are being used to treat NSCLC, three of them (Alunbrig [3], Tafinlar and Mekinist [4]) got their first approvals in 2017 [4]. According to their route of administration, they can be classified as orally or intravenously drugs. According to their mode of action, they can be classified into 4 categories: angiogenesis inhibitors [5], human EGFR inhibitors [6], tyrosine kinase inhibitors and PD-1 inhibitors [7]. Angiogenesis inhibitors are drugs that target and block the tumor blood vessel growth (angiogenesis). Two drugs that target vascular endothelial growth factor (VEGF) [8], a protein that helps new blood vessels to form, are FDA-approved to treat NSCLC and taken as an infusion into a vein (IV). Bevacizumab [9], was approved as a first-line treatment of patients with locally advanced, metastatic or recurrent NCCLC in combination with platinum-based chemotherapy [2]. Ramucirumab [10], was approved in combination with docetaxel for the treatment of patients with metastatic NSCLC with disease progression on or after platinum-based chemotherapy [11]. Human EGFR inhibitors are drugs that target and block the signal from the epidermal growth factor receptor (EGFR), a protein on the surface of cells that due to its overexpression in some NSCLC helps these cells to grow faster and divide [12]. One drug is FDA-approved to treat NSCLC and taken as an infusion into a vein (IV). Necitumumab [13], was approved in combination with gemcitabine and cisplatin for first-line treatment of patients with metastatic squamous NSCLC [14]. PD-1 inhibitors are drugs that block PD-1, programmed cell death protein 1, and thus activate the immune system to attack tumors [7]. Three PD-1 inhibitors are approved to treat NSCLC and taken as an infusion into a vein (IV). Pembrolizumab [15], was approved for the treatment of patients with metastatic NSCLC whose tumors express programmed death ligand 1 (PD-L1) with disease progression on or after platinum-containing chemotherapy [16]. It was further approved in 2016 for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 [17], and approved in 2017 in combination with pemetrexed and carboplatin for the treatment of patients with previously untreated metastatic NSCLC [4]. Atezolizumab [18], was approved for the treatment of patients with metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression prior to receiving atezolizumab [19]. Nivolumab [20], was approved for the treatment of patients with metastatic squamous NSCLC with progression on or after platinum-based chemotherapy. It was also approved in 2015 for the treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression prior to receiving Opdivo [21]. In 2016 FDA modified its dosage regimen for NSCLC [4]. Tyrosine kinase inhibitors include drugs that target cells with EGFR gene mutations [12], cells with T790M mutation [22], cells with ALK gene changes [23] or cells with BRAF gene changes [24]. Ten tyrosine kinase inhibitors are approved to treat NSCLC.

Three drugs are being used to treat NSCLC with EGFR gene mutations and taken as pills. These drugs are used alone as the first treatment for advanced NSCLCs that have certain mutations in the EGFR gene, which are more common in women and people who have not smoked [25]. Erlotinib [26,27] was approved for maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. It was further approved in 2013 for first-line treatment of metastatic NSCLC patients whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations [28]. In 2016 FDA modified its indication for treatment of NSCLC to limit use to patients whose tumors have specific EGFR mutations [4]. Afatinib [29,30], was approved for first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. Gefitinib [31,32], was approved for the treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

One drug is being used to treat NSCLC with T790M mutation and taken as tablet. EGFR inhibitors stop working during the treatment for most people, usually because the cancer cells develop another mutation in the EGFR gene such as the T790M mutation [22]. Osimertinib [33,34], an EGFR inhibitor that works against cells with the T790M mutation, was approved for the treatment of patients with EGFR T790M mutation-positive NSCLC, who have progressed on or after EGFR tyrosine kinase inhibitor therapy. It was further approved in 2017 for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, whose disease has progressed on or after EGFR tyrosine kinase inhibitor therapy [4].

Four drugs are being used to treat NSCLC with ALK gene changes and taken as pills. Some NSCLCs have a rearrangement in a gene called anaplastic lymphoma kinase (ALK), a change is most often seen in non-smokers (or light smokers) who have the adenocarcinoma subtype of NSCLC. The ALK gene rearrangement produces an abnormal ALK protein that causes the cells to grow and spread [23]. Drugs that target the abnormal ALK protein can often shrink tumors in people whose lung cancers have the ALK gene change. Although they can help after chemo has stopped working, they are often used instead of chemo in people whose cancers have the ALK gene rearrangement. Some of these drugs are useful in treating people whose cancers have changes in the ROS1 gene. Crizotinib [35,36], was approved for the treatment of patients with locally advanced or metastatic NSCLC that is ALK-positive. It was further approved in 2013 for the treatment of patients with metastatic NSCLC whose tumors are ALK-positive [4] and approved in 2016 for the treatment of patients with metastatic NSCLC whose tumors are *ROS1*-positive [37]. Ceritinib [38,39], was approved for the treatment of patients with ALK-positive, metastatic NSCLC with disease progression on or who are intolerant to crizotinib, and approved in 2017 for patients with metastatic NSCLC whose tumors are ALK-positive [4]. Alectinib [40,41] was approved for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. Brigatinib [42,3], was approved for the treatment of patients with metastatic ALK-positive NSCLC who have progressed on or are intolerant to crizotinib.

Two drugs are being used to treat NSCLC with BRAF gene changes and taken as pills. Some NSCLCs have changes in the BRAF gene, a human gene that encodes a protein called B-Raf that helps them to grow [24]. Two drugs that target this protein and related proteins are used to treat metastatic NSCLC if it has a certain type of BRAF gene change. Dabrafenib [43], is a type of drug known as a BRAF inhibitor, which attacks the BRAF protein directly. Trametinib [44], is known as a MEK inhibitor, because it attacks the related MEK proteins. A combination of both drugs was approved for patients with metastatic NSCLC with BRAF V600E mutation [4].

In summary

With 11 years old is the targeted therapy of lung cancer still young but promising with 16 FDA-approved drugs to treat NSCLC. The targeted therapy drugs have been developed to specifically target changes in the cancer cells, a process that improves the antitumor efficacy and reduces the systemic toxicity over the traditional chemotherapy. Such drugs have proven to be successful in treating lung cancer either in a single therapy or in combination with other drugs. Oral administration of many drugs is an additional advantage of this therapy. Last but not least, personalized drugs that address protease expression and gene mutations in tumor patients forms a strong logic for a drug candidate to obtain a market approval.

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