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A Comparative Study of Osimertinib and Pembrolizumab in the Treatment of Stage III Non-small Cell Lung Cancer: Mechanism and Clinical Implications

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Abstract. Lung cancer is known as one of the cancers that people are diagnosed with the most, so there are many treatments for lung cancer in recent years. This investigation focuses on the mechanisms and clinical implications of two medicines that are used to treat stage III non-small cell lung cancer, Osimertinib and Pembrolizumab. This comparative study shows the significant difference between the mechanisms of the two medicines, which Osimertinib is the representative of chemotherapy of cancer, and Pembrolizumab represents one example of immunotherapy. This work reveals some differences between the two methods of cancer treatment, the key mechanisms of the two kinds of medicine, and outlook the further investigation on its field.

Keywords: Lung cancer, Osimertinib, Pembrolizumab

1. Introduction

According to the data that was given from Global Cancer Observatory 2022 by World Health Organization, 2,480,675 of new cases and 1,817,469 of death number in a year had made lung cancer to be one of the cancers that kills the most people. Additionally, according to the data that was given from Cancer Incidence and Mortality in China, 2022, There were about 1,060,600 new cases of lung cancer with approximately 73.33% of cancer mortality rate [1]. And the article also pointed out that lung cancer is the most precious and usual among all the cancers in China [2]. In other countries such as the US, lung cancer has also been recognized as one of the most typical cancers in the population of cancer patients [3].

Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) are the two kinds of lung cancer overall [4]. Within the two kinds of lung cancers, NSCLC is more commonly appeared in the patients, which donates about 3/4 of the lung cancer patients' community [4]. In stage III NSCLC, the patient would have symptoms such as tiredness, coughing up blood, chest pain, hoarseness, chronic cough, shortness of breath, loss of appetite, wheezing [5], and knowing that the tumors cannot usually be able to be eradicated completely through surgery, but with the participation of chemotherapy, radiotherapy, targeted therapy, or immunotherapy [6].

In this investigation, I offer an overall view of the mechanisms of Osimertinib and Pembrolizumab that are used in this case, including their advantages, features and further clinical

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implications compared to other drugs.

2. Background information

The most universal subtype is lung adenocarcinoma (LUAD), as well as lung squamous cell carcinoma (LUSC) being the one after [1]. Research has found out that the mutations of Epidermal Growth Factor Receptor EGFR and Kirsten Rat Sarcoma viral oncogene homolog (KRAS), are responsible for regulating cell proliferation and its survival [1]. Consequently, mutations in EGFR or KRAS can result in incorrect cell growth or formation of cancer cells [1]. The structure of EGFR on cell membrane is shown below as Fig.1.

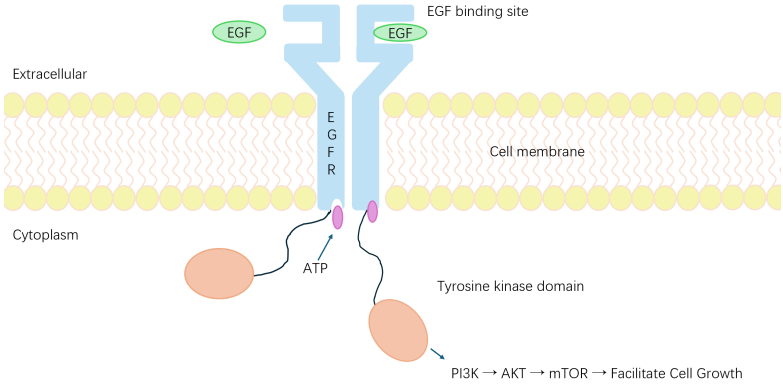

Figure 1. EGFR on cell membrane

For EGFR, the mutation types can be the absence of exon 19, as well as the L858R exon substitution [7]. Contrast with different race groups, research also discovered that these mutations happened more normally among the Asians [8].

Immune evasion is one of the hallmarks of cancer, which means the immune system does not provide anti-cancer response efficiently [9]. PD-L1 plays a role as a protein that stop attacking of T cells by binding with the DP-1 (PD-L1 receptor) on T cells, which are commonly turned on when the T cells are attacking too many cells [10]. As a result, cancer cells took advantage from it and evolved PD-L1 on their surfaces to escape from T cell induced anti-tumor activity [11]. The graphical mechanism is displayed as Fig.2.

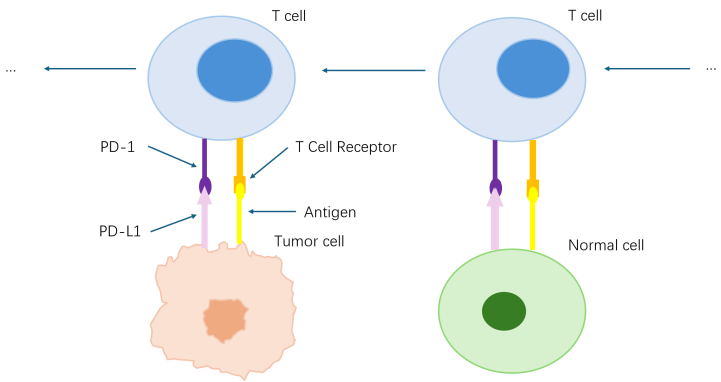

Figure 2. Cells express PD-L1 to avoid attacking from T cell

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3. Information on Osimertinib

3.1. Osimertinib as a chemical

Osimertinib, or Tagrisso, the brand name, is one of the targeted therapy drugs [12]. The IUPAC name of Osimertinib is N-[2-(dimethylamino)ethyl-methylamino]-4-methoxy-5-[[4-(1-methylindol-3-yl)pyrimidin-2-yl]amino]phenyl]prop-2-enamide [11], and the 2D chemical structure is given below as Fig.3.

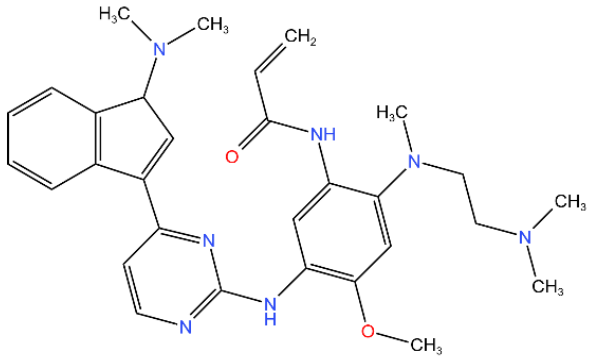

Figure 3. The chemical structure of Osimertinib in 2D

3.2. Mechanism of Osimertinib

Osimertinib is the third generation of epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) and has solved the problem of mutation T790M (can develop drug resistance) efficiently by forming an irreversible bond with the site, which the previous generations didn't achieve [8,13].

The mechanism of Osimertinib is to block the site that receipt ATP by forming an irreversible covalent bond with the site by the acrylamide group that is circled on Fig.4, so as Fig.5 shown, it would Inhibit EGFR kinase activity and downregulate downstream pathways such as PI3K-AKT and RAS-RAF to suppress cell growing [8].

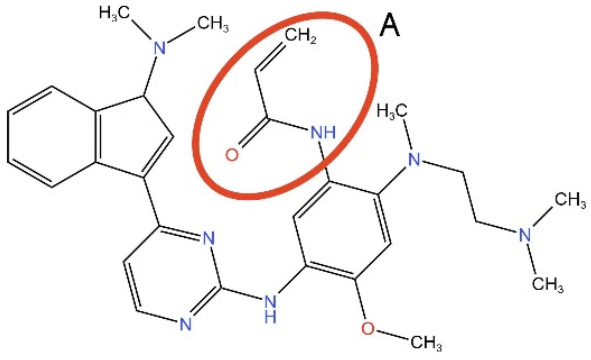

Figure 4. The chemical structure of Osimertinib in 2D, A shows the position of acrylamide group

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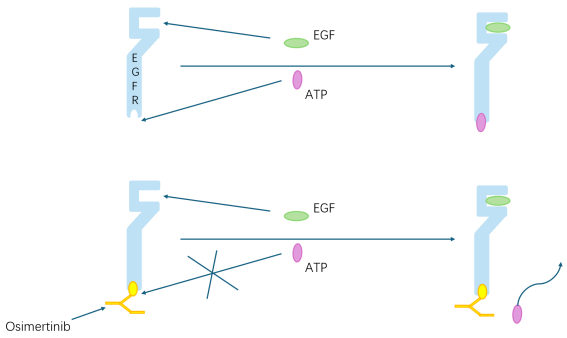

Figure 5. The mechanism of Osimertinib to suppress EGFR

Moreover, Osimertinib is also used in treating brain cancer due to its ability of penetrating blood brain barrier. The blood brain barrier is a system that consists of some types of cells, which can protect the brain from bacteria, viruses, and most giant molecules, as well as soluble chemicals [8].

4. Information on Pembrolizumab

4.1. Pembrolizumab as a protein

Pembrolizumab, or Keytruda, the brand name, is an immunotherapy drug [13]. It does not have an IUPAC name, because Pembrolizumab is a monoclonal antibody (mAb) [13], which can be simply described as a type of highly specialized antibody that recognizes a specific epitope, and they are cloned form the same B cell [14]. The 3D structure of Pembrolizumab is shown below as Fig.6.

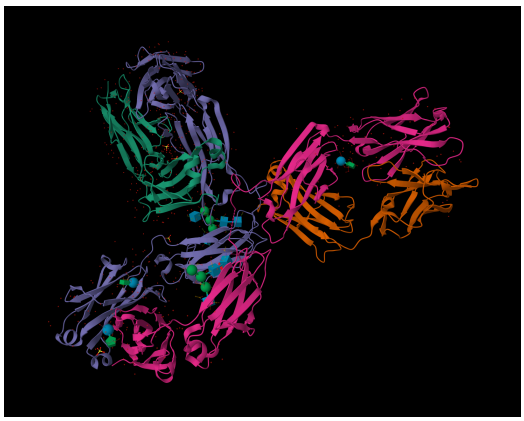

Figure 6. The 3D chemical structure of Pembrolizumab

4.2. Mechanism of Pembrolizumab

Pembrolizumab is a PD-1 inhibitor, it can obstruct the binding between PD-1 and PD-L1 so that the T cells will be activated to destroy cancer cells, which can be visualized as Fig.7 [11].

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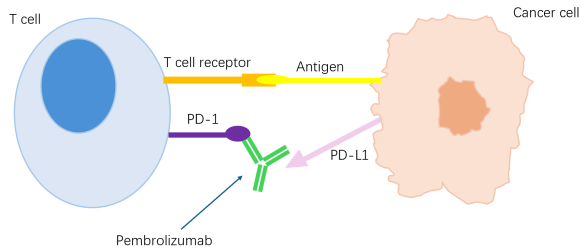

Figure 7. The mechanism of Pembrolizumab to obstruct the binding between PD-1 and PD-L1

According to Gandhi (2018), Pembrolizumab is allowed to be used in patients whose cancer cells express PD-L1 greater or equal to 1%, and as the proportion grows greater, the efficacy will be even better. In addition, research observed that Pembrolizumab can be utilized in combination with chemotherapy and radiotherapy to reinforce reaction rate [15,16].

5. Comparison of Osimertinib and Pembrolizumab

5.1. Clinical indication

Osimertinib is being used in EGFR mutation positive NSCLC, especially for postoperative adjuvant therapy or drug resistance [17,18].

Pembrolizumab is used for patients who have PD-L1 positive NSCLC and showing great effect on consolidation treatment after chemotherapy and radiotherapy [15,16,19].

5.2. Efficacy comparison

From the experiment funded by ADAURA, about 80% of patients displayed two years of Disease-Free Survival (DFS) in postoperative treatment, which is a very good percentage [17].

For Pembrolizumab, the experiment described the Progression-Free Survival (PFS) and the Overall Survival (OS)of patients who used Pembrolizumab were both longer compared to traditional chemotherapy [16].

5.3. Side effects & resistance

Osimertinib: Diarrhea, rash, QT prolongation (risk of irregular heartbeat), and C797S mutation is the most common drug-resistance mechanism [18,20].

Pembrolizumab: Immune-related adverse reactions (irAEs), including pneumonia, hepatitis, and endocarditis [11,13,15].

6. Conclusion & discussion

The mechanism of both drugs is different, which Osimertinib is a targeted therapy drug, while Pembrolizumab is an immunotherapy drug, so they are used in different situation. Therefore, the key to treating NSCLC is to determine the type of NSCLC such as through gene testing, immune markers screening, and so on. And further investigating direction could be working on drug combinations, drug-resistance mechanisms, and reducing toxicity.

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