The Role of Pembrolizumab (Keytruda) in Treating Non-small Cell Lung Cancer

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Abstract. Lung cancer also cause causes most of the cancer death cases around the world. In 2020, 1,796,144 people from all the world were estimated to die because of it. Lung cancer is responsible for one-fourth of all cancer death cases. There are many risk factors for lung cancer, including air pollution and cigarettes. Genes also play an important role in the pathogenesis of lung cancer. There are many types of treatment for it nowadays and they are used in different stages or different combinations. Treatment of NSCLC is influenced by the patient's overall health status, tumor stage, and pathological type. However, most of them have lots of side effects, such as bone marrow suppression, liver and kidney damage, etc. Compared to those treatments, immune checkpoint inhibitors less side effects. Pembrolizumab (Keytruda) is one of the inhibitors, which has a good performance in treating the NSCLC. Pembrolizumab inhibits the binding of PD-1 to PD-L1 and has shown good results in many clinical experiments. However, it also has limitations. As a result, this paper will introduce non-small cell lung cancer, Pembrolizumab (Keytruda), and its function in treating this disease.

Keywords: Pembrolizumab, Non-small Cell Lung Cancer, Treatment.

1. Introduction

There were 236,740 adults who got the lung cancer in 2021 in the United States, and 117,910 of them were men and 118,830 of them were women. Lung cancer also cause causes most of the cancer death cases around the world. In 2021, 130,180 death cases caused by it were estimated to occur in the US. In 2020, 1,796,144 people from all the world were estimated to die because of the lung cancer. Lung cancer is responsible for one-fourth of all cancer death cases. The male has a 5-year survival rate of 18%, while the female has a 5-year survival rate of 25%. About 80-85% of non-small cell lung cancers (NSCLC) are the main type of lung cancer [1]. There are many types of treatment for the lung cancer nowadays and they are used in different stages or different combinations, however, most of them have lots of side effects. Compared to those treatments, immune checkpoint inhibitors less side effects.

Immune checkpoints play a very important role in the immune system, which can recognize normal cells and abnormal cells. Immune checkpoint inhibitors are drugs that block different immune checkpoints or proteins to activate the immune system. Nowadays, more and more types of cancer can be treated by the immune checkpoint inhibitors. According to a recent study, the number of patients that immune checkpoint inhibitors can treat increased from 1.54% in 2011 to 43.63% in 2018. Additionally, estimates of the number of individuals who are able to respond to this type of medication increased from 0.14% in 2011 to 12.46% in 2018 [2]. So more and more people can get benefit from the immune checkpoint inhibitors.

Pembrolizumab (Keytruda), which is a type of drug of the immunotherapy, is one of the PD-1-targeting immune checkpoint inhibitors [3]. Nowadays, people often use that to treat NSCLC and melanoma skin cancer. It works by blocking the PD-1 and activating the T-cell in order to kill the cancer cells.

The basic facts of Pembrolizumab, non-small cell lung cancer, and Pembrolizumab's function in treating non-small cell lung cancer are introduced in this review.

2. Risk factors

Everyone can develop lung cancer if their lung cells are mutated or damaged, or if their gene is mutated. However, there are some risk factors that may increase the possibility to get the lung cancer. Smoking is one of the most important risk factors causing the lung cancer. According to the research, 70% of it is caused by a cigarette (figure 1). During the process of smoking, it will release over 5000 chemicals and most of them will cause the cancer. Those chemicals will spread around the whole body and sometimes they will damage the DNA. Also, some of them will make the cells unable to repair the DNA. Finally, the damage to the DNA will cause the lung cancer [4].

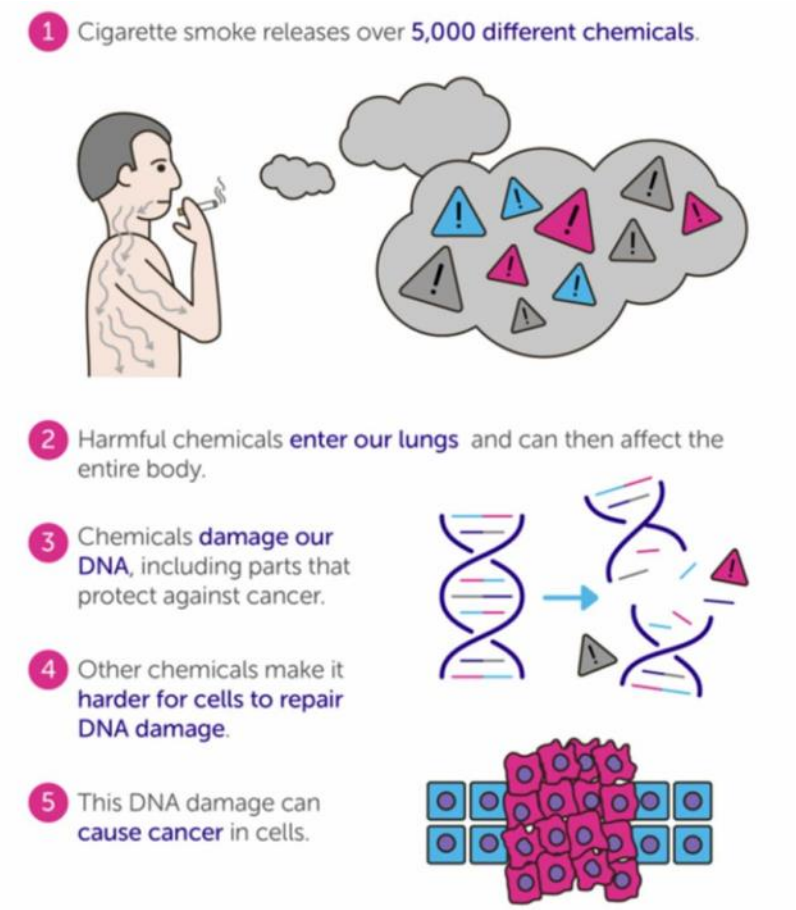

Figure 1. Smoking and lung cancer [4].

The air pollution can also result in the lung cancer. People's health will be impacted by the carbon dioxide, nitrogen dioxide, and sulfur dioxide in the polluted air. The air pollution causes about 10 percent of the lung cancer. Numerous minute particles that accumulate in the lungs as a result of breathing in polluted air disrupt healthy cells, damage DNA, and ultimately result in lung cancer. In Xuanwei (Yunnan, China), people are more likely to get the lung cancer, because it has very serious air pollution problems. Compared to the average lung cancer rate in China, the rate of lung cancer is 4-5 times greater [5].

Lung cancer will also develop if there is a history of the disease in the family. According to previous studies, a family history of it significantly raises the risk, 230 non-smoking patients with NSCLC had a family history in roughly 18% of the all cases. There will be some differences in the chromosomes, and the people with lung cancer are more likely to gain two or more chromosomes for each cell. In short, the family history of lung cancer may not make one get the lung cancer directly, however, the person with the family history is susceptible to get it compared to the people who live in the same environment [5].

3. The dangers of NSCLC

Cancer is uncontrolled and abnormal. Generally speaking, cells will die when they get damaged or old. However, the cancer cells won't. They will continue to expand and could eventually develop a tumor to pose a threat. Although NSCLC is treatable, its survival rate is not very high. The survival rate depends on the histopathological type of NSCLC that patients get. For the localized type, which means the cancer cells have not spread yet, its five-year survival rate is 64%. However, metastatic tumor, which spreads to the nearby area, only has a three-year survival rate of 37%. For the distant type has a five-year survival rate of about 8% [6,7]. One of the most prevalent cancers is NSCLC. According to the American Cancer Society, in the United States, there are around 228,150 new cases per year. People who die because of the lung cancer each year are even more than the combination of breast, colon, and prostate cancers. Meanwhile, the cancer cell will grow without control, spread around your body, and form a tumor, which may cause the threat to life.

4. The stage of the treatment

The treatment of NSCLC was affected by patients' overall health, and the stage. NSCLC has numerous stages, and each stage determines how it will be treated. However, other factors such as the patient's overall health can also decide the treatment. First, there is a system called the TNM system, which refers to "tumor," "nodes," and "metastasis." It is used to describe the development of the cancer. For example, Stage IA (T1N0M0), that means the tumor is in the stage 1, and there is no node and metastasis [8].

For the stage 0 of NSCLC, it does not have too many obvious symptoms, so it is also found accidentally. The early stage of NSCLC just has some effects on the lining layer of the airways, and the cancer cells have not spread yet, so patients just need to take the surgery. However, there are several types of surgeries such as Pneumonectomy, which removes the whole lung, and the final choice usually depends on the location of it and the patient's status [8]. For some patients who are not willing or suited to take the surgeries, other therapies such as the photodynamic therapy (PDT) and stereotactic body radiotherapy (SBRT) can also be used to treat the NSCLC.

For the stage 1 of NSCLC, it is divided into two types, which is Stage IA and Stage IB, and they are decided by the length of the tumor. There are several types of treatment for this stage, however, surgery is still a good choice for that. However, other types of treatment such as the chemotherapy and the radiation treatment can also treat the NSCLC of stage 1. But the best choice depends on the development of the tumor, nodes and metastasis [8].

The stage 2 of NSCLC, or localized cancer, which means that the lung may have the tumor, but there is no further metastasis. Surgery is still a good choice for this stage. However, after the surgery, a combination of therapies may still be done in order to prevent the tumor to form again [8].

The stage 3 of NSCLC, is that the cancer cells have begun to spread around the place it starts, which is described as "locally advanced." At this stage, a combination of treatments is performed, such as chemotherapy, immunotherapy, targeted therapy. Sometimes, the cancer of this stage may affect other parts of patients' bodies, so the patients may have the symptoms such as bone pain.

The stage 4 of NSCLC, which is the most advanced stage of the NSCLC, has already spread the cancer cells around your body and this stage is not curable. Since the tumor has spread to other regions, the symptoms of this stage will be more obvious. You may have the loss of memory, bone pain, weakness. The NSCLC of stage 4 cannot be cured completely, however, patients can receive the treatment to live longer. Conventional treatments can all be used in this stage and the final choice depends on the state of the patient.

5. The role of Pembrolizumab in NSCLC

A checkpoint protein, called PD-1, locates on the T-cell. It will work when it binds to the PD-L1. The combination of PD-1 with PD-L1 will prevent the T-cells from attacking that cells. However,

because some cancer cells also have the PD-L1, it may sometimes hide and prevent themselves from being attacked by the T-cells. Then, using certain inhibitors such as Avelumab (Bavencio) and Pembrolizumab (Keytruda) to target it, and enable the T-cell to destroy cancer cells. However, sometimes it will affect the normal cells and kill them mistakenly.

Another type of checkpoint protein, known as CTLA-4, is found on T-cells and gives the T-cells the ability to regulate the immune system. When the CTLA-4 binds with the monoclonal antibody such as Ipilimumab, the immune checkpoint will consider it as the normal cells. If CTLA-4 is blocked, immune checkpoints will consider it as an abnormal cell, and try to kill that cell. CD80 on cancer cells will bind to CTLA-4 to prevent them from attacking. Blocking CTLA-4 allows T cells to attack cancer cells.

Another checkpoint inhibitor on the immune cell is the LAG-3 inhibitor which also helps to check the immune system. It has a similar mechanism to the CTLA-4. The monoclonal antibody that binds to it is the Relatlimab. Additionally, it can be utilized to treat several cancers.

When getting the advanced NSCLC, and patients still have the normal EGFR and ALK gene, the Pembrolizumab (Keytruda) is often used along with the chemotherapy. When the surgery and the chemotherapy are not suitable, and patients' tumors are tested positive for the PD-L1, Pembrolizumab (Keytruda) is often chosen as the first treatment. Sometimes, the chemotherapy may not work, then it is time to use Pembrolizumab (Keytruda). Age can also decide the final treatment. The older patients (older than 62) usually have a higher response rate after receiving the Pembrolizumab treatment than the younger patients (younger than 62) because for every decade of age, the resistance to the Pembrolizumab will drop by 13%. An experiment with the mice also showed a similar result. After receiving the Pembrolizumab, the slower growth of the tumor was observed in the older mice, but not in the younger mice. As one of the front-line treatments of NSCLC, it shows almost no difference in the treatment for different races. In a study involving 74 white people with NSCLC, and 53 black patients, white patients got progression-free survival for 5.7 months, while the black patients got it for 5.9 months, which was quite close. The overall survival rate was 11.8 months and 12.4 months, which also did not show a lot of differences. The final result was also quite close for the patients with tumors that express PD-L1 in a high level (≥50%). The reason for using the chemotherapy alone with the Pembrolizumab (Keytruda) is that it can help to maximize the response to the cancer and result in the prolonged survival. The KEYNOTE-189 trial also showed that the patient who receives a combination of chemotherapy and Pembrolizumab (Keytruda) has a longer survival rate compared to the patients who only receive the chemotherapy [9]. An experiment indicates that the 12-month survival rate of NSCLC after using the pembrolizumab-combination group is 69.2%, while the one after using the placebo-combination group is 49.4%, which shows the great improvement of using the Pembrolizumab. For patients with advanced non-squamous NSCLC, pembrolizumab to platinum-pemetrexed chemotherapy is now regarded as one of the standard treatment [10]. Docetaxel is a drug of chemotherapy. For patients that express PD-L1 on at least 50% of their cells, receiving pembrolizumab 10 mg/kg will provide them with a longer survival time than receiving docetaxel. Meanwhile, there are less than 3-5 treatment-related side effects after the patients receive the pembrolizumab instead of receiving docetaxel.

6. The limitation of PD-1/PD-L1

Since it is an example of the immune system, its efficiency usually depends on the immune system. The limitation of it sometimes causes difficulties in treating the cancer. The first limitation is that there are not enough clinical trials for the children, so it is uncertain if the children can get the benefits. The second limitation is that the expression in tumors is heterogeneous. It is highly expressed in some of the tumors, instead of all the tumors and it will generally limit the effectiveness of the immune checkpoint inhibitors. The third limitation is that compared to adults, children usually have fewer mutations. The normal lung cancer usually exceeds 100/MB (one mutation per exome), however, the cases for the children are only about 0.1/MB, which means there are fewer mutations for the children.

Usually, the immune checkpoint inhibitors will work more effectively when there are more mutations because mutation will stimulate the T-cell to make more responses. So, it may not work well when the patients have less mutations. The reason for adults to get more mutations is that they are more likely to exposure to carcinogens, which will cause more mutations and finally result in the lung cancer. The fourth limitation is that children usually have less MHC than the adults [11]. MHC, which refers to a major histocompatibility complex, is a type of protein to help the immune system to recognize the cells [12]. Children usually do not have enough MHC, which will make the T-cell have fewer responses. Then the immune checkpoint inhibitors can not work well with the weaker immune system. The next limitation is that children usually have an immature immune system, which means the T-cell cannot respond well to the cancer. The last limitation is that when treating the lung cancer, patients usually need to receive the chemotherapy. However, after receiving the chemotherapy, children's immature immune systems will be weaker and get the immunosuppression. Without the response of the immune system, then the immune checkpoint inhibitors cannot work well at that time.

7. The advantage and the disadvantage

Immune checkpoint inhibitor is one part of the immune therapy. Sometimes it may work better than other treatments. Also, when using other treatments, immune checkpoint inhibitors may make the result more satisfying. Meanwhile, immune checkpoint inhibitors may bring fewer side effects than other treatments. After the treatment, the patient can have a better immune system, which can deal with the cancer better. By making the immune system has a higher efficiency to respond to the cancer cells, the immunotherapy is playing a more and more important role in the cancer treatment. As a developing technology, it has increased the average 5-year survival rate from 5.5% to 15%. Meanwhile, its response rate to the cancer is between 20 to 50% [13].

There could be some negative effects from Pembrolizumab (Keytruda) therapy because the immune system could mistakenly kill healthy cells. The lung, liver, kidney, skin, and some other parts of the body will experience negative effects. Some possible adverse effects include rash, hair loss, blood in the urine, cough, and chest pain. Although the side effect is sometimes common during therapy, it still relies on the histopathological type and patients' status. Also, the immune therapy is very expensive, the average cost in 2015 was $228,504, and the average cost in 2016 was $202,202, which is much more expensive than the chemotherapy.

8. Conclusion

NSCLC accounts for a higher case fatality rate, and many factors can contribute to this cancer. Smoking, gender and genetic factors play an important role in its occurrence and development. Different stages require different types of treatment and the final choice is also made according to the overall health and the age of the patients. Conventional clinical programs, such as surgery, radiotherapy and chemotherapy, have the problems of large trauma and high recurrence rate. Seriously endanger the patient's life treatment and prognosis. With the rise of immunotherapy, this approach may become the possibility of a cure. Pembrolizumab, as one of the immune checkpoint inhibitors, has shown its great importance when treating the NSCLC. For example, when it is used with the chemotherapy or the surgery, it can increase the efficiency of the treatment. After the treatment, patients may have a better immune system and longer survival rates. However, Pembrolizumab still has a lot of disadvantages, it may sometimes let the T-cells kill the normal cells mistakenly and cause the unavoidable and unknown side effects. Meanwhile, its high cost may create huge financial pressure for a lot of families. There are still some ways that people can improve. In the future, it is necessary to further deepen the research on the immune system to understand its mechanism of killing tumor cells, which will help to propose intervention targets. At the same time, corresponding animal model tests and clinical trials also need to be in progress.

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