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Current and Developing Treatments to Target EGFR for NSCLC

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ABSTRACT

Lung cancer is amongst the most diagnosed cancers with a relatively low five-year survival rate of around 20 percent. Currently, the most frequent first-line treatments for lung cancer, more specifically non-small cell lung cancer, consist of chemotherapy, radiation therapy, target therapy, and immunotherapy. However, challenges such as the high cost of treatment, drug resistance, and immunosuppressive tumor microenvironment make it difficult to treat the cancer effectively. While researching ways to overcome these challenges, new treatments involving CAR-T therapy which has shown promise in treating blood cancer, and CRISPR which has shown the precise targeting of genes are being developed intensively. This review will delve into the EGFR gene, and how targeting it could improve the prognosis due to its prevalence in patients diagnosed with NSCLC. Overall, this review will detail the advantages and disadvantages of each of the current treatments for NSCLC and present new treatments like CAR-T and CRISPR for NSCLC.

Introduction

Lung cancer, one of the deadliest types of cancer, was estimated to project a total of 127,070 deaths in the United States in 2022 (Miller et al., 2008). This number has increased to more than 1.8 million deaths worldwide. 80-85% of these lung cancer cases are attributed to non-small cell lung cancer (NSCLC), a disease where malignant cells develop in lung tissue mostly because of smoking 80% of the time (Zappa & Mousa, 2016a). This alarming data showcases the importance of targeting the most common genetic mutations that lead to NSCLC, the most prevalent form of lung cancer, with the most effective treatments available to improve the prognosis of these patients.

The branch of lung cancer is typically divided into two types: NSCLC and small cell lung cancer (SCLC). The main statistical difference between the two is that NSCLC comprises about 85% of lung cancer cases including adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma, and SCLC makes up 15% of other lung cancer cases (Basumallik & Agarwal, 2023). On a cellular level, NSCLC cells are larger and grow slower compared to SCLC which has a smaller cell size and grows faster. This paper will focus on NSCLC as it impacts a greater number of people.

The most common symptoms are fatigue, loss of appetite, shortness of breath, chest pain, and blood in sputum all of which are burdensome and heavily impact a patient's quality of life (Iyer et al., 2014). When these symptoms can be observed and NSCLC is suspected to be the diagnosis, patients often go through a series of tests including tumor biomarker detection, chest x-rays, CT scans, sputum cytology, and many other tests to ensure a proper assessment and treatment of cancer (PDQ Adult Treatment Editorial Board, 2002).

Along with the current treatments known to be effective in treating NSCLC such as chemotherapy, radiation therapy, target therapy, and immunotherapy, other treatments are also developing. Chimeric Antigen Receptor (Car)-T cell therapy, which has been effective in treating leukemia, lymphoma, and recently myeloma,

and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and CRISPR-associated protein 9 (Cas9) technology which has been used to edit the genome are both promising new treatments for NSCLC.

EGFR Mutations in NSCLC

The Epidermal Growth Pathway Receptor (EGFR) is an 1186 amino acid transmembrane glycoprotein (Ogiso et al., 2002) that is involved in many cell signaling pathways that control the way cells divide. When mutated, however, the EGFR protein can get stuck in an on position, leading to abnormal cell growth (Rude Voldborg et al., 1997). The EGF receptor, located at the cell surface, consists of three regions, the extracellular ligand-binding region, a transmembrane region with a single hydrophobic anchor sequence, and most notably the intracellular region with tyro-sine kinase activity which plays a big role in cell differentiation and proliferation (Rude Voldborg et al., 1997b). Mutations to EGFR are most commonly related to tumorigenesis in lung cancer, glioblastoma, and breast cancer (Sigismund et al., 2018).

In NSCLC specifically, the prevalence of EGFR mutations in NSCLC patients is around 32.3% (Zhang et al., 2016). The EGFR mutation occurs 45% and 40% of the time through the exon 19 deletions and exon 21 substitutions (Stewart et al., 2015). Overall, the EGFR mutation is significantly associated with light smokers (Tanaka et al., 2010) and is more commonly found in those of Asian descent (Graham et al., 2018).

Target treatments for the EGFR mutation have been developed mainly through the form of tyrosine kinase inhibitors (TKIs) that inhibit tumor-growing ability in the EGFR mutated cells. This treatment has been effective, but a lot of these patients develop drug resistance, so researchers are finding new ways to overcome this issue to continue treating patients with TKIs (Tang & Shrager, 2016a).

Current Treatments for NSCLC

For stages I and II of NSCLC, where the cancer has yet to spread or has spread little to the lymph nodes near the lungs, surgery is often a viable option for treatment. Most times, the surgeon will be able to remove most of the tumor in which case the patient will follow with adjuvant therapy to reduce the chance that the cancer will return (Zarogoulidis et al., 2013).

After stage III of NSCLC, where the cancer has spread to a lot of the surrounding lymph nodes, current treatments generally include chemotherapy, radiation therapy, targeted therapy, immunotherapy, and more. A very common treatment for all cancers is chemotherapy drugs that use chemicals to rid of fast-growing cells inside the body. Common NSCLC chemotherapy drugs are Cisplatin, an alkylating agent, that damages the DNA of cells to stop them from reproducing (Brown et al., 2019), and Paclitaxel, also known as Taxol, which regulates mitosis and leads cells to apoptosis (Walsh & Goodman, 1999). These two drugs are used specifically in NSCLC because of their ability to effectively target tumors. Along with Cisplatin and Taxol, other chemotherapy drugs are used in combination to increase the chances of killing all the cancer cells.

Although chemotherapy is often a reliable first line of defense against cancer and is relatively cheap compared to other types of treatments, there are a few downfalls that come with this therapy. The most common side effects are hair loss, fatigue, weight changes, nausea, and skin changes. These side effects are caused by chemotherapy's difficulty targeting specific cells in the body which damages normal cells and can very much limit the lifestyle of patients who go through this type of treatment (Altun & Sonkaya, 2018). Another downfall is drug resistance. Since chemotherapy is usually a regulated treatment that follows a set schedule, it often leads to drug resistance which occurs when cancer cells contain molecular changes that make the cells insensitive to the drug after several dosages. This acquired resistance can be a result of many situations such as the activation

of another oncogene after treatment, altered expression of drug targets, and changes to the tumor microenvironment (Wang et al., 2019). Researchers are trying many different approaches to administering these drugs such as combining the treatments or switching them off to delay the emergence of resistance (Luqmani, 2005).

Radiotherapy, also known as radiation therapy, is also currently a viable treatment option for NSCLC. Radiotherapy uses high-energy beams to destroy the DNA within the cancerous cells to rid them from the body. By itself, radiation therapy is beneficial to those who do not respond to surgery or chemotherapy and those whose tumors are rather localized. This therapy can also be used to reduce the size of large tumors before it is operated on to increase the success rate of the surgery. Radiation therapy has been shown to reduce the recurrence of localized lung cancer tumors but doesn't necessarily improve overall survival rates by itself (Kim & Jeter, 2023)

Target therapy can also be used to treat NSCLC, especially in the later stages. Compared to chemotherapy, target therapy is more precise and is more effective in killing cancerous cells. Target therapy works with the immune system to destroy cells and interrupt signals that cause cancer cells to replicate continuously (Ke & Shen, 2017). Targeted drugs are more easily tolerated by the body because healthy cells are not killed which reduces the plethora of side effects that chemotherapy causes. Like all drugs, however, target therapy isn't for everyone. Biomarker testing is often conducted to identify specific genetic mutations that may determine if target therapy would be beneficial to a patient. With EGFR mutations, there are target agents that have been successful in increasing the survival rates for patients (Zappa & Mousa, 2016b). Some drugs that have already been approved to target EGFR include Iressa (for patients with exon 19 deletion and exon 21 substitutions), Gilotrif (for patients with a change in EGFR), Enhertu, Rybrevant, Tagrisso, Tarceva, and Vizimpro (Gerber, 2008). In addition to this, if the biomarker testing determines that the patient is fit for more than one targeted therapy, they may be able to receive additional treatment.

Like other treatments, there are challenges to target therapy as well. Due to the specific nature of target therapy and the personalized testing needed to determine the treatment for the patient, the latest target therapy is one of the most expensive treatments for lung cancer. This can be burdensome to a lot of cancer patients. Additionally, similarly to chemotherapy, cells can also become resistant to the therapy; however, this can mostly be bypassed when multiple target therapies work together. These drugs can also be hard to develop based on the patients' target's structure and function in the cell which makes this treatment not suitable for all patients (Gerber, 2008)

Another treatment for NSCLC is immunotherapy. Immunotherapy uses the body's defense system to fight off cancer (Zappa & Mousa, 2016b) It boosts the immune system so that it is more effective in recognizing cancer cells. In contrast with chemotherapy which kills both health cells and cancer cells, immunotherapy works to target only the cancer cells by training the patient's immune system for detection.

Some challenges have arisen regarding the tumor microenvironment including cancer-associated fibroblasts, tumor-associated macrophages, and myeloid-derived suppressor cells that drive the cells to form solid masses that resist apoptosis, proliferation, and invasion (Yang et al., 2016).
In other words, the tumor microenvironment prompts the development of cancer and acts like a shield against effector immune cells (Tormoen et al., 2018). Furthermore, because Immunotherapy is quite new, it is quite costly for patients, and it is not guaranteed to work well for all patients.

New Proposed Treatments for NSCLC

CAR-T therapy has been quite effective in the treatment of blood cancers. The therapy works by collecting a patient's T cells and engineering them to produce CARs on the surfaces of the cells to target specific antigens. However, in solid tumors, many issues arise with the lack of mobility in the immunosuppressive tumor microenvironment (Sterner & Sterner, 2021). Researchers are trying to bypass this issue by creating "armored CARs" that are resistant to the hostile tumor microenvironment, engineering probiotic bacteria to guide CAR-T cells

to tumors (Vincent et al., n.d.). The single chain variable fragment (scFv) expressed by the CAR-T is used to direct the t-cells to different areas. In NSCLC specifically, the biomarker mesothelin is highly expressed in lung cancer so the scFv, if engineered to target the mesothelin in the cell membrane, can be more effective in treating tumors using CAR-T (Ochi et al., 2021).

Another new technology that could be used is CRISPR/Cas9. CRISPR/Cas9 is a gene editing technology that allows for the manipulation of the genome. There are many potential uses for this new technology such as the correction of genetic disorders or HIV. In cancers specifically, there has been interest in using CRISPR/Cas9 to modify patient's T-cells which can be reintroduced into the patients (Redman et al., 2016)Also CRISPR/Cas9 could be combined with CAR-T therapy to manipulate the CAR-T cells into resisting the tumor microenvironment.

For the EGFR mutation in NSCLC, there has been development for personalized molecular surgery that will work to repair or destroy the EGFR mutated genes using virus-delivered with the CRISPR/Cas9 system. This way the therapy is much more specific in that it will target the EGFR's tyrosine kinase domain and introduce a stop codon to block the EGFR's protein translation, thus stopping its oncogenic activity (Tang & Shrager, 2016b)This type of treatment is still new and being tested but it is hoped to be permanent and effective in personalized treatment.

Conclusion

With treatments still being developed for NSCLC, it's hard to conclude which are the most beneficial to NSCLC patients. On a case-to-case basis patients and their providers can choose which therapy to use and if they want to combine therapies for a better prognosis. Current treatments for NSCLC such as chemotherapy, target therapy, radiation therapy, and immunotherapy have their advantages and disadvantages. Most of the treatments for cancer are disadvantaged by drug resistance resulting from the changes in the tumor microenvironment and altered expression of drug targets. This is a challenge; however, researchers are continuously trying to conquer this. For those who have the EGFR mutation, TKIs, and target therapies are more effective in irradicating cancer. Additionally, there are still new and innovative treatments such as CAR-T therapy in solid tumor cancers, and new combinations such as CAR-T therapy and CRISPR/Cas9 being tested for the benefit of cancer patients. With the help of these treatments, NSCLC patient outcomes will have better prognosis in the future.

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