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Current available treatments for NSCLC

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Abstract. Lung cancer is one of the most prominent forms of cancer and ranks as the deadliest of disease afflicting humanity. To tackle this issue, a variety of treatment approaches have been devised to counteract this disease. This review aims to illustrate the mainstream curative and palliative treatment methods in managing non-small cell lung cancer, the most common subtype of lung malignancies.For each treatment method, we have investigated its mechanism, classifications, and techniques involved as well as the clinical success of these treatments. Furthermore, we have also included the reasoning behind each treatment plan, including both quality of life as well as overall survival benefits for the patient.

Keywords: Non-small cell lung cancer, Therapeutic Vaccination, Molecularly Targeted Therapy, Tyrosine Kinase Inhibitors, Immunotherapy

1. Introduction

Among all of the harmful diseases, Lung cancer stands as one of the most prevalent and deadly adversaries to human health. More than 100,000 lives are lost each year due to this affliction, and humanity arduously researches and engineers new treatment methods. This extensive review attempts to shed light on the currently available approaches for managing non-small cell lung cancer (NSCLC), the most common type of lung cancer malignancy.

This paper will be delving deep into the mechanisms, classifications, techniques, and clinical outcomes of each therapeutic and palliative treatment. Through specific topics include the realms of surgery, chemotherapy, molecularly targeted therapy, and therapeutic vaccinations, this paper will attempt to unwrap the enigmas within these medical interventions in the relentless pursuit of saving lives.

Lung cancer's far-reaching implications demand our unwavering attention, and this review aims to shine a light on the path towards improved understanding and contribute towards the goal of engineering more effective treatments.

2. Surgery

Surgery is the most common treatment method for early-stage non-small cell lung cancer (NSCLC) and is often used in combination with chemotherapy or molecularly targeted therapy as adjuvant therapies. Patient's overall health dramatically increases with the help of surgery; while patients who decline surgery have an estimated 5-year overall survival of 11%, those who underwent surgical resection at the same stage have an overall survival of 60-80%. The most common surgical methods include lobectomy, segmentectomy, and wedge resection.

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2.1. Surgical diagnosis

There are two main objectives in surgical treatment for lung cancer, which are diagnostic and therapeutic. Local treatment such as surgery for advanced NSCLC is rarely completely curative and has high risks of recurrence, therefore diagnosis is essential for narrowing down the patient's specific prognoses [1]. Additionally, the removal of a substantial amount of lung tissue is essential to identify the stage of the NSCLC, which is important for determining which adjuvant therapy strategy is required.

Preoperative evaluation may be attempted before surgery but is often not accurate. However, this process is important as it can be used to differentiate between early stage (Stage I and Stage II) and locally advanced disease (Stage III). Some evaluation techniques for this procedure including cervical mediastinoscopy and anterior mediastinotomy can investigate whether cancer is present in lymph nodes. Surgery is highly suggested for cancers at Stage I and Stage II, but other treatment methods such as radiotherapy may be considered for patients at Stage III or with other more dangerous complications.

For surgical diagnosis, additional tissue containing lymph nodes may be removed to aid the diagnostic to ensure more accurate cancer staging. Nevertheless, there exists a divergence of opinions among sources regarding whether or not a more aggressive removal of lymph node tissue has benefits in enhancing diagnostic accuracy and improving overall survival rate.

2.2. Lobectomy

Lobectomy involves resection of an entire lobe through surgery and is generally considered to be the gold standard for NSCLC surgical treatment. Statistics from the large ACOSOG Z0030 trial suggest that disease-free survival at 5 years was 68% for Stage I or Stage II patients who underwent Lobectomy [2]. However, Lobectomy surgeries are not completely risk-free and may lead to side complications such as atrial fibrillation, prolonged air leaks, as well as pneumonia [3].

Video-assisted thoracoscopic surgery (VATS) is a technique that can be used in combination with other surgery methods. It involves thoracoscopic visualization through video technology rather than open surgery, where the surgeon views the procedure directly [4]. The VATS technique shows similar complications that arise during surgery; however, these problems occur at lower rates when compared with open surgery. A multitude of quality-of-life changes are experienced by the patient, including earlier recovery, less degeneration of pulmonary function, relieved pain as well and reduced length of hospitalized stay.

Another recently developed technique utilizes robotic technology for resection surgery. The advantages of robot-assisted surgery are quite similar to those of VATS, which include smaller incisions that inflict less operative trauma upon the patient. This is primarily due to open surgery requiring incisions around the ribs to allow a better field of view for the surgeon. With VATS and robotic surgery, these extra cuts are not required. Additionally, the robotic instruments have wider ranges of motion compared to human surgeons, allowing for more precision during the surgical procedure [1].

2.3. Sublobar resections

Sublobar resections are distinguished from lobectomies by the extent of lung tissue removal. While lobectomies remove an entire lobe, sub-lobar resections excise a portion of lung tissue that is less than a full lobe. Sublobar resections can be further categorized into more specific procedures, including segmentectomies and wedge resections.

Sublobar resections seem to have more lung function preserved, however, the morbidity rate between lobectomies and sublobar resections are quite similar, because sublobar resections are shown to have a significantly higher chance of recurrence. Therefore, lobectomies are the widely suggested treatment for patients in the early stages of NSCLC. Sublobar resections are generally recommended as a form of compromise procedure for patients who lack lung function or for whom general health forbids them from undergoing lobectomies.

The procedure for segmentectomy is very similar to that of lobectomy, except a small portion of the lobe is removed rather than the entire lobe. Multiple sources agree that there is no significant difference in rates of survival or recurrence for Stage I NSCLC between lobectomies and segmentectomy, but this

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statistic changes as the size of the tumor increases with recurrence rates increasing drastically for non-Stage I segmentectomy [1].

2.4. Wedge Resection

Wedge resection involves the resection of an even smaller piece of lung tissue. This means that the rate of recurrence and the rate of success are incomparable compared to the other major surgery methods commonly used for NSCLC treatment. However, edge resections are essential to patients with specific conditions such as life-threatening comorbidities.

3. Chemotherapy

Chemotherapy treatment involves the use of drugs that target cells with fast replication. While cancer cells unquestionably constitute the primary target of chemotherapy because they are characterized by their abnormal and uncontrolled replication, our bodies also contain specific cells that are designed to replicate quickly, such as our skin cells, hair cells, as well as the lining of our intestinal tract. This means that chemotherapy has significant side effects which can damage not only cancer cells but also our healthy living cells. Damaged hair cells and epithelial intestinal cells lead to common chemotherapy side effects such as hair loss and nausea. Chemotherapy is often utilized before or after surgical operations to either reduce the size of the tumor before the operation or to kill hidden cancer cells which were hidden.

Adjuvant chemotherapy involves chemotherapy used after surgical treatment. Undetected small metastases may lead to dangerous complications if left unaddressed after a potentially curative surgery, therefore, adjuvant chemotherapy is essential for a comprehensive and complete recovery. In a study of 5 trials investigating adjuvant chemotherapy, researchers found that there was a 5.4% absolute increase in survival of 5 years after chemotherapy treatment [5].

Cisplatin-based chemotherapy can be used in conjunction with a variety of other drugs in adjuvant therapy including pemetrexed, vinorelbine, docetaxel, or gemcitabine. In one study, experimenters found that cisplatin chemotherapy used with pemetrexed was less toxic compared to the other drugs.

Neoadjuvant therapy is used before surgery, and data for this therapy are mixed and generally inconclusive. Most studies agree that the benefits of neoadjuvant chemotherapy include early treatment of micrometastases as well as possible down-staging. Several large-scale experiments identified that the absolute survival benefit of neoadjuvant chemotherapy is approximately 5-6% at 5 years, which is similar to that of adjuvant chemotherapy [5].

4. Molecularly Targeted Therapy

Molecularly targeted therapies are different from other curative procedures as they do not have significant side effects. This is because they specifically target biomarkers that are heavily overexpressed within tumor cells, and these biomarkers are generally not present in healthy somatic cells. However, the role of molecularly targeted therapies in treatment remains under heavy debate. Presently, molecularly targeted therapies often assume a similar role as chemotherapy, frequently serving as adjuvant therapy.

Tyrosine kinase inhibitors (TKIs) target receptor tyrosine kinases (RTKs) which are normally involved in cell growth. However, when these RTKs harbor mutations, their function shifts towards preserving and expanding tumor tissue by signaling the need for rapid proliferation, angiogenesis, and well as tumor migration [6]. By inhibiting these receptor sites using TKIs, we can block their signal transmission, thereby preventing tumor growth and proliferation.

4.1. Epidermal Growth Factor Receptor Inhibitors

The most popular targeted therapy is Epidermal Growth Factor Receptor Inhibitors, which target the mutated EGFR as a biomarker. Statistics show that approximately 15% of NSCLC patients carry mutated EGFR [7]. The EGFR mutation can be targeted through either monoclonal antibodies or tyrosine kinase inhibitors (TKIs). Current molecularly targeted therapy utilizes the third generation

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osimertinib, although first and second-generation erlotinib, gefitinib, afatinib, and dacomitinib are still available. EGFR TKIs seem to have a significant effect on a patient's progression-free survival, but not as much on their overall survival in a study comparing TKIs with platinum-based chemotherapy [8][9].

4.2. Anaplastic Lymphoma Kinase Inhibitors

Anaplastic lymphoma kinases (ALKs) are another receptor site that can act as a biomarker for molecularly targeted therapies. The expression of ALK is generally associated with accelerated tumor growth, and approximately 5% of NSCLC patients possess a translocated ALK gene. The first-generation ALK TKI known as Crizotinib outcompeted chemotherapy in terms of progression-free survival as well as response rate, and its effectiveness was demonstrated in another study, showing stable disease progression in 33% of the patients [7]. The second generation of TKIs include Ceritinib, Brigatinib, and Alectinib, and have shown better responses in patients compared to the first-generation ALK TKI called Crizotinib. For instance, alectinib proved to be more effective and less toxic, with a 12-month event-free survival of 68.4%, whereas the first generation of ALK TKI crizotinib only achieved 48.7%. Additionally, studies have shown that while crizotinib shows a median progression-free survival of 10.9 months, alectinib exhibits 34.8 months of progression-free survival.

5. Therapeutic Vaccinations

The mechanism of therapeutic vaccination is to improve the response of the innate and adaptive immune system against cancer cells. Vaccines can trigger cellular and antibody reactions against tumor-specific antigens or tumor-associated antigens. Additionally, vaccine-induced humoral responses can trigger the clonal expansion of cytotoxic T cells which can target and kill cancer cells. The specificity of increasing cytotoxic T-cells is one of their main advantages compared to other forms of curative treatment as they cause minimal to no complications for the patient.

While it was initially believed that the immune system could only target and destroy non-self-pathogens, researchers found that they could target human cancer cells through the introduction of tumor-specific or associated antigens. While the immune system does act to promote tumor growth through the secretion of anti-inflammatory cytokines or interfering with cancer-detecting mechanisms, it is still possible to induce an immune response specifically against tumor cells in a cancer patient. This is often done with the help of immunoadjuvants which could enhance the immune response.

For the immune response to be able to specifically target cancer cells, the immune cells must first recognize the tumor-specific or tumor-associated antigens. When phagocytic cells such as macrophages take up the antigens administered through the bloodstream in the form of vaccination, the macrophages will express these antigens within their major histocompatibility complex II (MHC II). These macrophages act as antigen-presenting cells (APCs) alongside with activated dendritic cells to present the foreign antigen to cytotoxic and helper T cells. While cytotoxic T cells can directly destroy cancerous cells, helper T cells carry other roles such as promoting inflammation through secretion of various cytokines such as interleukins or tumor necrosis factors as well as activating B cells. Activated B cells can differentiate into plasma cells, which can produce antibodies that are specifically against the tumor-associated or specific antigen.

5.1. Allogenic Tumor Cell Vaccines

Allogenic tumor cell vaccines are built from irradiated or otherwise weakened cancer cells that are no longer able to replicate abnormally and uncontrollably. These cells still contain their tumor-specific marker on their surface, which APCs can use to identify and target cancer cells due to their allogenic nature. One example of an allogenic tumor cell vaccine used in NSCLC is known as Lucanix or the Belagenpumatucel-L vaccine. This vaccine includes tumor-associated antigens from four different cancer cell lines, allowing them to reach a wider range of patients. Additionally, this vaccine also targets transforming growth factor beta 2 (TGF-beta 2) to counteract its detrimental effect against other treatments [10]. TGF-beta 2 is an anti-inflammatory cytokine that has suppressive effects on vital immune cells in the anti-tumor immune response including natural killer, cytotoxic as well and dendritic

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cells. By vaccinating against this transforming growth factor, antibodies will bind to these factors as soon as they are secreted, effectively nullifying their purpose, and allowing for better anti-tumor responses.

5.2. Anti-idiotype vaccines

Anti-idiotypes stand out as distinctive compared to other vaccines because they frequently involve the administration of monoclonal antibodies rather than foreign antigens.

In this case, the monoclonal antibodies act as antigens themselves: the immune system recognizes the idiotypes on the monoclonal antibodies as a foreign signal and can launch an immune response against the original antigen, which is the tumor-associated antigen used to manufacture the monoclonal antibody itself. An example of an anti-idiotype vaccine used in NSCLC curative treatment is known as Racotumomab. This vaccine targets NeuGcGM3, which is a glycoprotein not expressed in healthy somatic cells. An immune response against the NeuGcGM3 protein will be able to also destroy tumor cells that carry this tumor-associated antigen.

5.3. Peptide Vaccines

Whilst other vaccines utilize complex mechanisms, peptide vaccines are relatively simple, including only a short chain of amino acids derived from a tumor-associated antigen. APCs will be able to pick up these antigens and cause an immune response against them. In CIMAvax-EGF vaccines, an immune response is triggered against epidermal growth factors. This vaccine utilizes the same mechanism as the EGFR TKI, but instead of blocking the receptors for EGF, this vaccine uses the immune system to produce antibodies against EGF, prohibiting the EGF-EGFR mechanism from unfurling. This peptide vaccine produces the same effect as the molecularly targeted therapy and has a longer-lasting nature conferred by memory cells produced from the immune response.

5.4. Liposomal Protein-based Vaccines

Liposomal vaccines are constructed from liposomes, which are small globules of fat droplets. These liposomes generally hold a recognizable antigen that the immune system can identify as a foreign signal factor. Some liposomes are designed to mimic the structure of pathogens, meaning the bodily immune cells will target them more aggressively. Additionally, due to the lipid composition of this vaccine, they are readily taken up by APCs which allow the immune reaction to be triggered faster and be more vigorous compared to other vaccines. Stimuvax is a liposomal vaccine currently used to treat NSCLC and enlists a cell surface protein known as mucin 1 which is commonly overexpressed in cancers [10]. Under regular circumstances, mucin 1 purely acts as a protective barrier. However, once mutated in cancer cells, mucin 1 can be overexpressed, which can lead to accelerated tumor development. Furthermore, mucin 1 can also undergo altered glycosylations, allowing cancer cells undetected by the immune system. By targeting mucin 1 as a biomarker, the immune system will be able to detect hidden tumor cells more effectively.

5.5. Viral-based vaccines

Viral-based vaccines are constructed from a modified version of an attenuated virus. These vaccines rely on the viruses' ability to stimulate an immune response. By modifying the surface proteins, we can pinpoint the immune system against a tumor-specific antigen. The TG4010 vaccine utilizes the viral-based vaccine technology by harnessing an attenuated version of the Ankara virus and implementing the aforementioned mucin 1 cell surface protein as a tumor-associated antigen. Additionally, the viral vector is also engineered to express the IL-2 interleukin, which aids in the process of activating the immune response [11].

6. Immunotherapy

Immunotherapies are a group of treatment procedures that make use of the body's immune system to fight diseases. Here we briefly introduce one specific form of immunotherapy known as immune

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checkpoint inhibitors (ICIs). ICIs function by inhibiting pathways that limit immune cell function. In standard immune responses, immune checkpoints are pivotal because they prevent the T cell from over activating. However, in cancer patients, the tumors may secrete additional immune checkpoints and weaken the T cell response, which leads to no prohibition of tumor growth. One example of an immune checkpoint is the pathway of the programmed cell death protein 1 (PD-1). When PD-1 joins with its receptor, it causes the inactivation of T cells and would drastically weakens their ability to fight tumors [12]. However, if this pathway is blocked using drugs or monoclonal antibodies, the T cells will have a much stronger response for a prolonged period. Unfortunately, not all patients gain similar benefits from ICI treatments. The mechanisms behind immune checkpoints and their pathways are still largely studied and therefore ICIs are currently not a treatment used widely.

7. Conclusion

A wide array of treatment procedures has been produced in an attempt to combat NSCLC, one of the most prevalent forms of cancer. This article has overviewed the main treatment methods currently employed as well as the mechanisms of their function. However, many of the treatments listed above are still under heavy testing, especially in fields like immunotherapy and molecularly targeted therapy. Even in fields in which no prominent research is conducted, constant innovations allow a better understanding of cancer and its management. In the quest to combat lung cancer, one of humanity's most formidable adversaries, a wide array of treatment strategies has been meticulously designed and implemented. This article has elucidated the predominant curative and palliative approaches for non-small cell lung cancer (NSCLC), the most prevalent manifestation of this malignancy.

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