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Immunotherapy in the treatment of non-small cell lung cancer (NSCLC) - analysis of epidemiology and cure – review

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Summary
Cancer is the second leading cause of death in Poland. Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for over 85% of all cases. Cancer incidence and mortality trends observed in the world and also Poland for many years, have been the resultants of changes associated with exposure to tobacco smoke carcino-gens (active smoking). Until recently, chemotherapy was the main treatment for NSCLC patients. Currently, thanks to the development of numerous research centers around the world, there are several methods of treating patients, which leads to the extension of cancer patients' lives and the improvement of their quality. The immune system plays an important role in controlling and eradicating cancer.

Immune checkpoint inhibitors (ICPs) have shown clear persistent responses and represent the emergence of a new approach to treating patients with NSCLC.

PD-1 inhibitors and PD-L1 inhibitors are a group of checkpoint inhibitors being developed for the treatment of cancer. Programmed cell death 1 (PD-1) is an inhibitory receptor expressed by activated T cells that down modulates effector functions and limits the generation of immune memory. Immunotherapy with monoclonal antibodies targeting with PD-1 and PD-L1 has become standard of care for an increasing number of indications. However, many patients with metastatic non-small cell lung cancer (mNSCLC) experience disease progression after first- and second- line treatment; therefore more treatment options are needed for these patients. Due to the specific characteristics of cancer immunotherapy and the rapid advances in this field, clinical guidelines for the use of these drugs are needed, including patient selection, response monitoring, careful observation of side effects, and biomarker testing.

Aim

The literature was searched to evaluate recommendations for drug initiation for targeted immunotherapy in non-small cell lung cancer (NSCLC). The evidence-based recommendations are designed to help doctors incorporate immune checkpoint inhibitors into the treatment plan of NSCLC patients. The aim of the review was also to check the latest data on the epidemiology of non-small cell lung cancer morbidity in order to compare the effectiveness of treatment over several years. The aim of the study is to review the standards of NSCLC treatment in terms of effectiveness, safety and patients' quality of life.

Materials and methods

World literature and scientific articles have been reviewed. The PubMed and Google Scholar databases and the National Cancer Registry in Poland were searched in July and August 2020. We used medical terms (MeSH) "non-small cell lung cancer", "immunotherapy", "ICPs", "durvalumab ". No language restrictions were added.

Conclusion

Advanced non-small-cell lung cancer is still a challenging disease. Chemotherapy and EGFR or ALK tyrosine kinase inhibitors are well-established options. Immunotherapy with immune-checkpoint inhibitors significantly improves survival both in first- and second-line treatment. Generally, it can be stated that the function of CTLA-4 and PD-1 receptors is to inhibit the activity and proliferation of T lymphocytes. However, monoclonal antibodies against negative CTLA-4 or PD-1 receptors (ICPs) eliminate their inhibitory effect on T lymphocytes. In the case of PD-1, the same effect can be achieved by blocking the PD-L1 ligand.

Immunotherapy has more advantages than chemotherapy. First of all, it is characterized by low cytotoxicity in relation to healthy cells and long-term cure rate in patients with even advanced cancer. Some caution should be exercised in analyzing the results of studies, as immunological treatment is characterized by high inter-individual variability in response to therapy, sometimes a large extension of treatment effects over time, and the possibility of transient progression before final tumor regression. Antibody-related side effects usually appear 8-10 weeks after initiating therapy, they are not serious, but relatively common (up to 60% of cases). Despite the encouraging results of previous studies, it is necessary to find objective markers for estimating the benefits of treatment, to reduce the amount of side effects and normalise the prices of new drugs.

Key words: immunotherapy, NSCLC, epidemiology, PD1, PDL-1, oncology

Introduction

Lung cancer carries serious medical, psychosocial, economic and social burdens. (1) Globally, lung cancer is the leading cause of cancer-related deaths, accounting for nearly 20% of all cancer-related deaths. In most cases, patients present with advanced or metastatic disease at the moment of diagnosis. (2) There are two main types of lung cancer and they are treated very differently. Firstly non- small cell lung cancer (NSCLC) and secondly small cell lung cancer (SCLC). About 80% to 85% of lung cancers are NSCLC. The main subtypes of NSCLC are adenocarcinoma, large cell carcinoma, and squamous cell carcinoma. These subtypes are grouped together as NSCLC because their treatment and prognosis (outlook) are often similar. (3) Histologically, the most common subtype of NSCLC is adenocarcinoma (ADC). (2)

Non-small cell lung cancer (NSCLC) is often diagnosed in the advanced stages of the disease when it cannot be cured. In recent years, new agents have been developed that enhance the host's immune response against cancer. (4) One of the groups of immunomodulatory drugs that modify the immune system are monoclonal antibodies. Negative receptors, such as Cytotoxic T Cell Antigen 4 (CTLA-4) and Programmed Cell Death protein 1 (PD-1), reduce the level of cell stimulation by other receptors, inhibit the activation and proliferation of T cells. The function of these receptors is the elimination of autoreactive immune cells, which have not been destroyed in the mechanism of central tolerance, and the protection of inflamed tissues in the body. Tumours are expressing negative receptor ligands and they avoid recognition by the immune system. Antibodies action involves blocking CTLA-4 and PD-1 receptors, restoring the ability of lymphocytes to recognize and respond to tumor antigens. (5) These agents enhance immunological antitumor activity by breaking down tumor immune tolerance. (6) Nivolumab is an anti-PD-1 receptor inhibitory monoclonal antibody that can prolong the survival of NSCLC patients with a manageable toxicity profile. Therefore, nivolumab has been approved in the US and Europe as a second-line drug in advanced NSCLC.

Epidemiology

Globally:

Lung cancer (both small cell and non-small cell) is the second most common cancer in both men and women (not counting skin cancer). In men, prostate cancer is more common, while in women breast cancer is more common. Lung cancer mainly occurs in older people. Most people diagnosed with lung cancer are 65 or older. The average age of people when diagnosed is about 70. (3)

Lung cancer is the leading cause of cancer death among both men and women, making up almost 25% of all cancer deaths. Each year, more people die of lung cancer than of colon, breast, and prostate cancers combined. (3)

In Poland:

In 2017, once again, the number of deaths among women caused by lung cancer exceeded the number of women who died due to breast cancer (by over 1155). In the male population, a decrease of morbidity and mortality of lung cancer has been observed for almost 15 years, which should be attributed primarily to the decline in the percentage of smoking men in recent decades.
Lung malignant neoplasms are still the dominant neoplastic cause of death in men, accounting for about 30% and determining the course of the mortality curve representing all male neoplastic diseases. (7)

The structure of cancer incidence in men and women: (Fig. 1, 2)

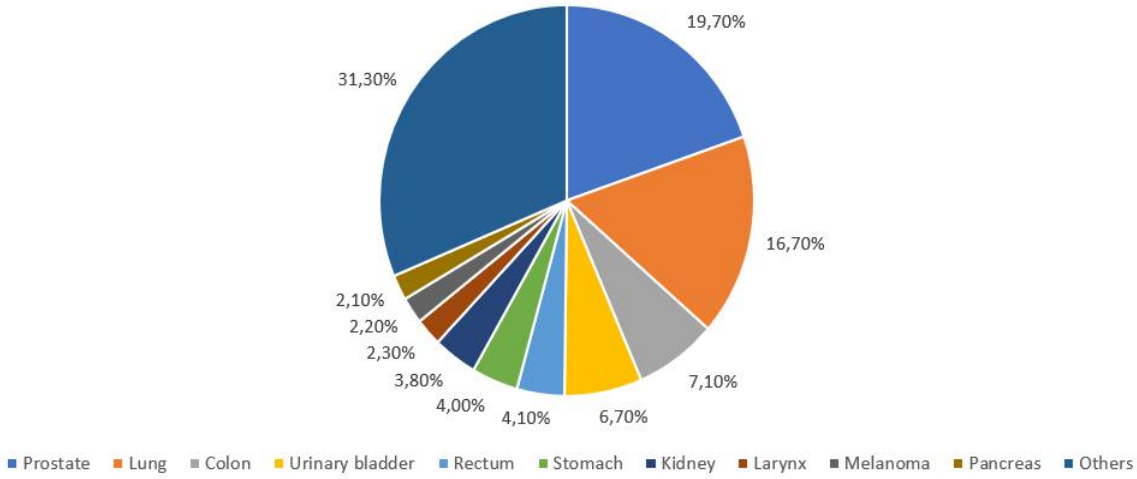

Figure 1. The structure of incidence, males

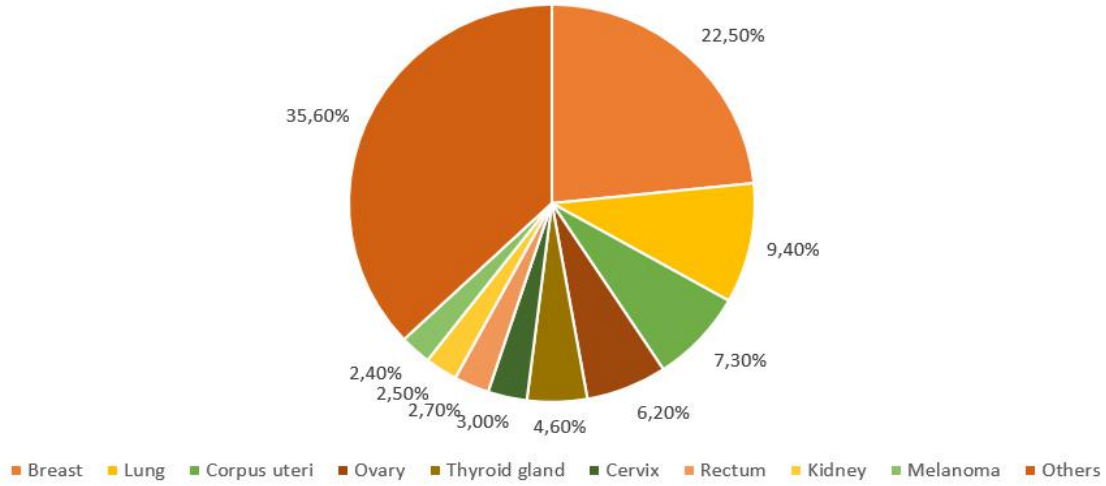

Figure 2. The structure of incidence, females

Structure of cancer deaths in women and men: (Fig. 3, 4)

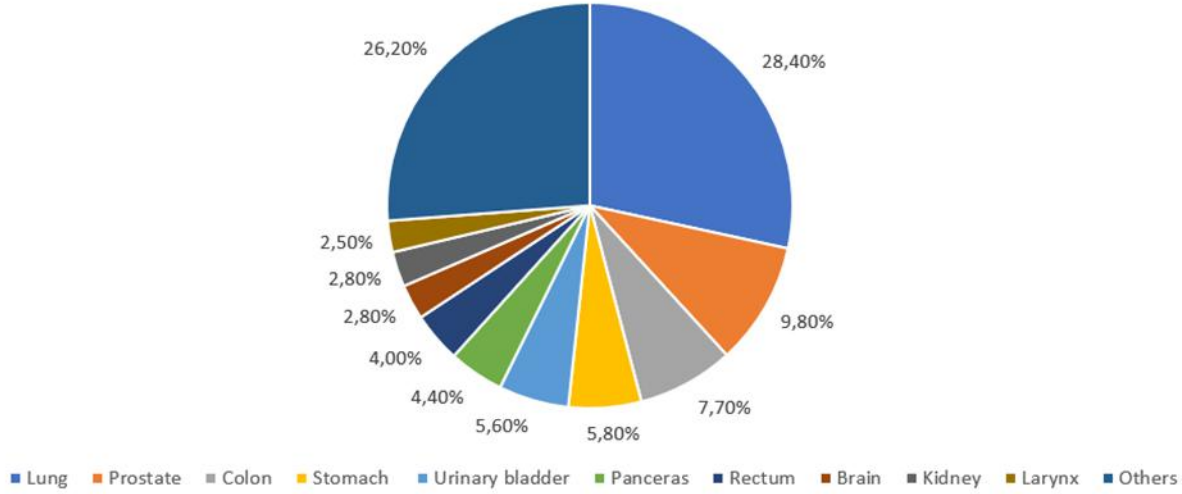

Figure 3. The structure of deaths, males

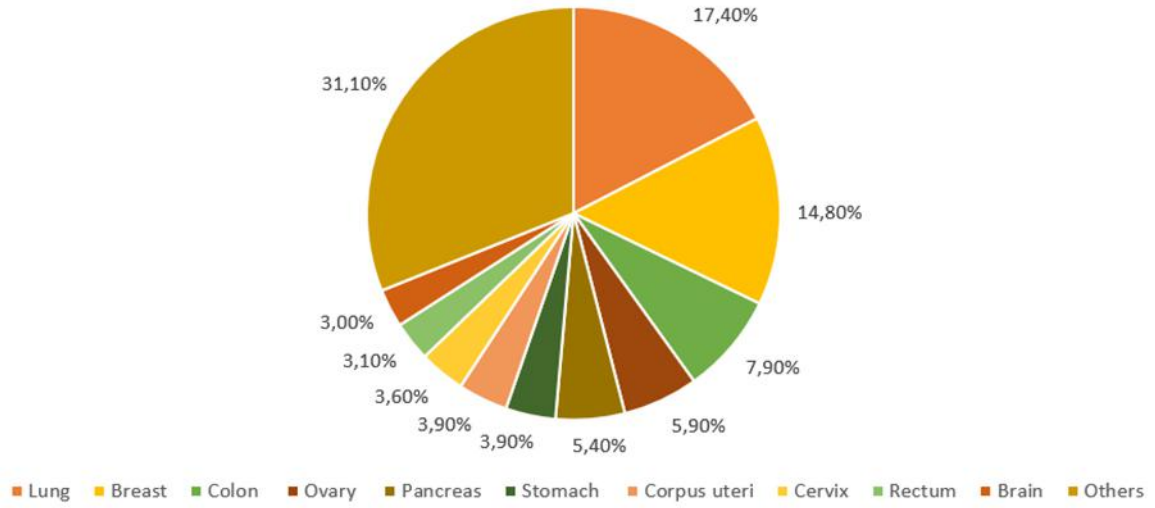

Figure 4. The structure of deaths, females

In the female population, the leading tumor sites are still the breast, lung and large intestine (colon and rectum).

Overall, the chance that a man will develop lung cancer in his lifetime is about 1 in 15 and for a woman, the risk is about 1 in 17. These numbers include both smokers and non-smokers. For smokers the risk is much higher, while for non-smokers the risk is lower. (3) In European countries, one in five cases of cancer is caused by smoking. This addiction is the cause of over 80 percent of all incidence cases of laryngeal and lung cancer (8)

Types of treatment

Lung cancer is treated in several ways, depending on the type of lung cancer and how far it has spread. People with non-small cell lung cancer can be treated with surgery, chemotherapy, radiation therapy, targeted therapy, or a combination of these treatments. People with small cell lung cancer are usually treated with radiation therapy and chemotherapy. (Fig. 5)

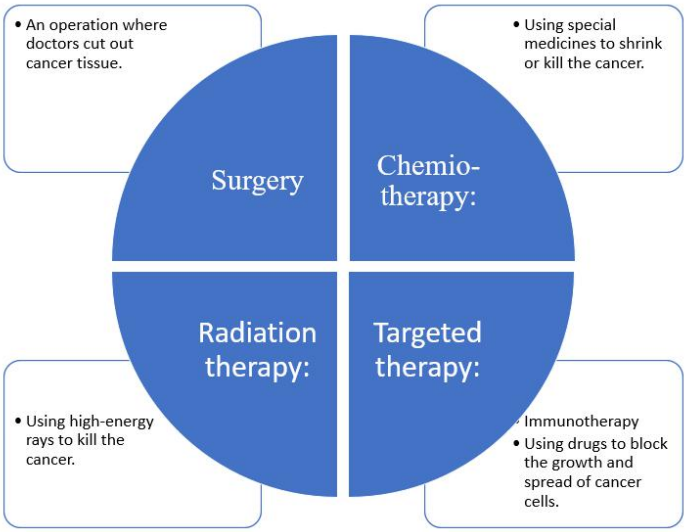

Figure 5. Types of treatment

Immunotherapy

Cancer immunotherapy is an alternative way of treatment in many early as well as advanced stages of carcinomas. Immune treatments depend on drugs that interact with the human immune system by escalating its tumour-fighting activity, providing immune system components and multiple other mechanisms. PD-1 inhibitors and PD-L1 inhibitors are a group of checkpoint inhibitors being developed for the treatment of cancer. PD-1 and PD-L1 are both proteins present on the surface of cells. Immune checkpoint inhibitors are emerging to a front-line treatment for several types of cancer. Immunotherapy with monoclonal antibodies (MoAbs) targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and the programmed death-1 receptor (PD-1) and its lig and PD-L1 has become standard of care for an increasing number of indications. (Tab. 1)

Drug	Action
Ipilimumab	anti-CTLA4
Tremelimumab	anti-CTLA-4
Nivolumab	anti-PD1
Pembrolizumab	anti-PD1
Durvalumab	anti-PD-L1
Atezolizumab	anti PD-L1

Table 1. Examples of immunomodulating drugs

The neoplasms which have already been studied with very different results include mainly melanoma, lung cancer and renal cell carcinoma, and others, such as breast, colon, ovarian cancer and numerous hematological cancers (Tab. 2) (9)

Ipilimumab	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab
• Metastatic melanoma • Adjuvant therapy stage III melanoma	• Metastatic melanoma • 2nd line metastatic NSCLC • 2nd line metastatic RCC • Classical Hodgkin's disease • Recurrent or metastatic SCCHN • Locally advanced or metastatic UCC	• 2nd line metastatic NSCLC (PD-L1 ≥1%) • 1st line metastatic NSCLC C (PD-L1 ≥50%) • 1st line metastatic NSCLC C in combination with pemetrexed + carboplatin • Classical Hodgkin's disease • Locally advanced or metastatic UCCc	• Locally advanced or metastatic UCC • 2nd line metastatic NSCLC	• Locally advanced or metastatic UCC

Table 2. Approved indications for ICPis (NSCLC, non-small-cell lung cancer; PD-L1, programmed death ligand 1; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck, UCC urothelial carcinoma)

Checkpoint inhibitors targeting the programmed cell death ligand 1 (PD-L1)/programmed cell death 1 (PD-1) pathway confer improvements in survival over standard-of-care therapies in NSCLC and other tumor types, and are now approved in several countries**.** (10) The most valuable method of immunotherapy in patients with advanced non-small cell lung cancer (NSCLC) is the use of immune-checkpoint inhibitors, which include programmed death receptor type 1 (PD1) inhibitors — pembrolizumab and nivolumab — as well as an inhibitor for PD1 ligand (PD-L1) atezolizumab. (11) In 2018, atezolizumab was registered in the

European Union for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. (11) So far, four immune checkpoint pathway inhibitors have been approved by the United States Food and Drug Administration (FDA) for use in patients with NSCLC: nivolumab and pembrolizumab, both targeting the programmed cell death-1 (PD-1) receptor, as well as atezolizumab and durvalumab, targeting the anti-programmed death- ligand 1 (PD-L1). In addition, complementary diagnostic tests measuring PD-L1 were approved as a predictive biomarker in the tumor microenvironment to assist in selecting patients for treatment. Determining which patients benefit from PD-1 / PD-L1 targeted immunotherapy remains an important clinical issue, particularly in view of the autoimmune toxicity of these drugs. (1,12,13) Immune checkpoint inhibitors are the standard of care for second-line treatment in advanced NSCLC, and pembrolizumab should be considered a standard first-line treatment in NSCLC patients with a good performance status whose tumors have PD-L1 expression $\geq 50\%$. PD-L1 status determined by immunohistochemistry should be considered a reflex biomarker, along with EGFR mutation and ALK translocation, in guiding treatment of front-line patients with advanced NSCLC. (12)

Due to the increasing number of indications (Table 1) for the use of drugs used in immunotherapy, more and more patients will be exposed to these drugs, with the risk of toxicity associated with these therapies. Toxicities from immune checkpoint inhibitors (ICPis) can be divided into infusion reactions and immune- related adverse events (irAEs) or adverse events of special interest (AEoSI). (9) Antibody-related side effects usually appear 8-10 weeks after initiating therapy, they are not serious, but are relatively common (up to 60% of cases). (5) The use of anti-CTLA-4 and anti-PD-1/PD-L1 antibodies is associated with side effects known as immune-related adverse events (irAEs). Immune-related adverse events affect in the dermatologic, gastrointestinal, hepatic, endocrine, and other organ systems. (14)

Rash and mucosal irritation are the most common and usually the earliest adverse reactions (irAE) associated with checkpoint inhibitors. Dermatological toxicity occurs in almost 50% of patients treated with ipilimumab. Checkpoint blockage rashes often appear as slightly erythematous, reticular, and maculo-papular. Alopecia and vitiligo (alopecia and vitiligo) may appear, but they happen less frequently. (15) You can then use topical creams with corticosteroids or antipruritic drugs (hydroxyzine hydrochloride or diphenhydramine hydrochloride), while in severe cases, oral GCS is used. (14) Antibodies that block PD-1 / PD-L1 can also cause oral mucositis and / or dry mouth symptoms. (16)

Diarrhea is another side effect seen in patients undergoing treatment with antibodies that block checkpoints. Diarrhea/colitis with CTLA-4 blockade is more common than with PD-1/PD-L1 blockade. In severe cases or situations in which symptoms do not improve with oral corticosteroids, hospitalization for intravenous corticosteroids, hydration, and electrolyte management are required. (14)

Hepatotoxicity occurs occasionally in patients treated with a checkpoint blocker, usually as manifested only by elevated laboratory parameters of the liver enzymes (increased aspartate aminotransferase (AST), aminotransferase (ALT) and, less commonly, total bilirubin). It usually occurs in less than 10% of patients using ICPs. (17)

Immunotherapy can also adversely affect the pituitary gland, adrenal glands, and thyroid gland. These effects are often accompanied by non-specific symptoms such as nausea, headache and fatigue.
Pituitary gland inflammation (pituitary inflammation) and hypothyroidism are the most common endocrinopathies and are thought to typically occur in up to 10% of patients treated with CTLA-4 blockade. (18) Therefore, it is worth remembering that when imaging the size of the tumor, attention should be paid to the enlargement of the pituitary and other glands as well as other biochemical determinants of endocrinopathy (adrenocorticotropic hormone [ACTH], thyroid stimulating hormone [TSH], follicle-stimulating hormone, luteinizing hormone, growth hormone, prolactin). Less frequently involved organs are lungs, eye, kidney, pancreas, hematologic syndromes and neurologic syndromes.

Conclusion

In recent years, progress has been made in cancer immunotherapy by the development of drugs acting as modulators of immune checkpoint proteins, such as the cytotoxic T-lymphocyte antigen-4 (CTLA4) and programmed death-1 (PD-1), two co-inhibitory receptors that are expressed on T cells upon activation. However, immune checkpoint blockade can lead to the breaking of immune self-tolerance, thereby inducing a novel syndrome of autoimmune/autoinflammatory side effects, designated as “immune-related adverse events,” mainly including rash, colitis, hepatitis, and endocrinopathies. Althought their exact prevalence and mechanism are unclear. Therefore, despite the satisfactory effects of the therapy, the patient should be closely monitored for these side effects of the therapy.

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Conflicts of Interest:

The authors declare no conflict of interest

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