Review article

The current state of knowledge on small cell and non-small cell lung cancer and the position of durvalumab immunotherapy in lung cancer treatment

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ABSTRACT

Lung cancer is the second most frequently diagnosed cancer and the leading cause of cancer-related deaths in the world. These statistics make lung cancer one of the most important targets for modern medicine.

The identification of multiple risk factors, including tobacco smoking, has been fundamental in understanding the disease. Late-stage detection is a significant contributor to the high mortality rate of lung cancer. Nonetheless, the role of screening is still debatable. The selection of therapy is primarily based on distinguishing between small-cell and non-small cell lung cancer. Despite the major differences in treatment, in both types in specific situations the treatment involves durvalumab – a monoclonal antibody targeting the programmed cell death ligand 1 molecule, which is often present on tumor cells and protects them against the patient's immune system. The efficacy of durvalumab has been demonstrated in two randomized, multicenter clinical trials.

The aim of this study is to summarize the current state of knowledge about lung cancer and durvalumab. Despite the current 5-year survival rate of 19% in lung cancer, the development of immunotherapeutics such as durvalumab may be the key to improving the unfavorable prognosis of lung cancer in the future.

Key words: PD-L1, immunotherapy, durvalumab, neoplasm, oncology, SCLC, NSCLC

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INTRODUCTION

Cancer is the second leading cause of mortality worldwide, surpassed only by ischemic heart disease [1]. According to GLOBOCAN estimates for 2020 [2], lung cancer constitutes the second most frequently diagnosed malignancy worldwide, with 2,206,771 new cases (1,435,943 men and 770,828 women), and accounts for the highest proportion of cancer-related deaths (1,796,144 deaths). Therefore, a concerted effort is required to develop effective methods for the diagnosis and treatment of lung cancer. Over the years, multiple therapeutic strategies have been developed for lung cancer management. In this report, we aim to provide an essential overview of the complex subject of lung cancer. Of particular significance is the role of durvalumab, a crucial drug used in the treatment of both major histological subtypes of lung cancer, namely small cell (SCLC) and non-small cell lung cancers (NSCLC). Thus, we present the role of durvalumab in the current approach to lung cancer treatment.

RISK FACTORS

Many risk factors of lung cancer have been discovered. Notably, smokers are at a significantly higher risk, with a 20-fold increase compared to non-smokers [3]. Moreover, the incidence of lung cancer rises with age, with approximately 85% of cases diagnosed in patients over 55 years old [2].

DIAGNOSIS

Coughing, shortness of breath, hemoptysis, and chest pain are the most common symptoms of lung cancer. Less commonly, loss of appetite, weight loss, fatigue, elevated body temperature, laboratory abnormalities and paraneoplastic syndromes are observed [4, 5]. As with most neoplasms, diagnosis of lung cancer requires histopathological examination. Positron emission tomography – computed tomography (PET-CT), node biopsy, magnetic resonance imaging (MRI) or computed tomography (CT) (including the head, a frequent site of metastases) are also used for cancer staging [6–8].

CLASSIFICATION

Lung cancers can occur in two forms – non-small cell lung cancer (NSCLC), which comprises 85% of lung cancers, and small cell lung cancer (SCLC), which comprises 15% of lung cancers. Additionally, NSCLC can be further classified into three primary types: adenocarcinoma (40% of lung cancers), squamous cell carcinoma (25–30% of lung cancers), and large cell carcinoma (5–10% of lung cancers). These types further fall into multiple clinical subtypes [9, 10].

As for the staging of lung cancers, the current classification utilized is the 8th edition of the TNM classification. The stage (I–IV) of the cancer depends on three parameters – T (tumor), N (nodes), and M (metastases). The T parameter is mostly dependent on the size of the tumor and the structures it infiltrates, while the N parameter is contingent on the involvement of specific lymph nodes. The M parameter depends on the presence of distant metastases and their location [11].

The division into NSCLC and SCLC, as well as the stage of the neoplasm, play a crucial role in determining the appropriate treatment protocol.

SURVIVAL

The 5-year survival rate for lung cancers stands at 19%. The survival rate is 23% for NSCLC and 6% for SCLC. Although the development of treatment methods has led to an increase in survival rates, the progress has been slower compared to other cancers. This could be attributed to the fact that lung cancer is usually diagnosed in the late stage, which results in a poorer prognosis [3, 12, 13].

SCREENING

Mortality depends largely on the stage at which cancer is diagnosed and treated. As cancer progresses, mortality increases rapidly – in patients diagnosed in 2003–2009, the calculated 5-year relative survival rate was 54% for cancer in local stage, 26% for the regional stage, and 4% for the distant stage [14, 15]. Due to these poor outcomes, efforts have been made to identify screening methods that allow for the early detection of neoplasms in individuals with risk factors for their development. The National Lung Screening Trial (NLST) on a group of 53,454 patients showed the superiority of using low-dose computed tomography (20% mortality reduction) over chest radiography (6.7% mortality reduction) ($p < 0.02$) [16, 17]. The randomized trial of Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON), conducted on 15,822 patients at high risk of lung cancer, revealed a 26% reduction in deaths from lung cancer in people screened with low-dose computed tomography after 10 years of follow-up, compared to the non-screened group [18–20]. The Multicentric Italian Lung Detection (MILD) randomized study from 2019 (4,099 participants) demonstrated a 58% decrease in lung cancer mortality and a 32% decrease in all-cause mortality after 5 years in patients with

risk factors who received low-dose computed tomography compared to the non-screened group [21]. Another randomized study conducted in the same year, the German Lung cancer Screening Intervention (LUSI), examined 4,052 patients with risk factors and showed a significant reduction in lung cancer mortality after an average follow-up time of 8.8 years in women who received low-dose computed tomography compared to non-screened women. However, this study did not show statistical significance in men or in all patients evaluated [22].

Sputum cytology and chest radiography did not show a sufficient value as screening tests [23, 24]. Despite the promising results of low-dose computed tomography, there is still no perfect consensus worldwide regarding screening of patients at high risk of lung cancer. This is due to the disadvantages of the method, such as high cost, exposure to radiation, or a high rate of false-positive results [25, 26].

TREATMENT

The management of lung cancer is a multifaceted process that is primarily determined by the categorization of the disease as either SCLC or NSCLC.

SCLC

The approach to treating SCLC is determined by the initial classification into limited SCLC and extensive SCLC. Typically, SCLC is diagnosed in its advanced stage and is not amenable to surgery. However, chemotherapy is highly effective initially, but relapses occur in the majority of cases even when there is a good response to chemotherapy.

The guidelines for treating SCLC can be broadly categorized into three main groups, which vary in some aspects: the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for SCLC [27, 28], the Chinese Society of Clinical Oncology (CSCO) Lung Cancer Guidelines [29], and the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for Metastatic SCLC [30–32].

Surgical treatment is possible only in patients with the disease at an early stage – T1-2N0M0 (according to NCCN and CSCO) or T1-2N0-1M0 (according to ESMO). In these cases, postoperative radiotherapy (PORT) is required [33].

Simultaneous chemoradiotherapy is so far the most effective treatment in patients with unresectable cancer [32]. According to the ESMO guidelines, patients with performance status (PS – WHO/ECOG scale) of 0-1 and T1-4N2-3M0 or T1-4N1-3M1 require concurrent chemoradiotherapy. NCCN and CSCO guidelines recommend concurrent chemoradiotherapy in patients with PS of 0-1/2 and limited SCLC T0-4N0-3M0 or extensive SCLC T1-2N0M0 [32].

The current standard of chemotherapy for advanced stage cancer is the platinum-etoposide (PE) combination. This combination has been shown to be at least as effective as the combinations previously used, but less toxic [34–36]. Immunotherapy is added to PE during induction and maintenance. Humanized monoclonal anti-programmed death-ligand 1 (PD-L1) antibodies – durvalumab and atezolizumab are used there. Adding these drugs to PE has been shown to have a beneficial effect on the survival of patients [37–40].

Most patients with extensive SCLC receive chemotherapy. Sequential chemotherapy in SCLC involves the introduction of radiation therapy, depending on the effect of the chemotherapy used initially [32].

Prophylactic cranial irradiation (PCI) is associated with a decreased risk of symptomatic brain metastases and an increased overall survival. Not all patients are eligible for PCI. The group that should be assessed for eligibility for PCI are patients with low PS and impaired neurocognitive functions who respond to first-line treatment [41].

NSCLC

Whenever possible, surgical excision is the best therapeutic option for NSCLC. Eligibility for surgery is based mainly on tumor stage, PS, presence of comorbidities, and lung function [40].

When NSCLC is stage I or II and there are no contraindications for surgery, the surgical treatment should be performed, and, in the case of stage II cancer, with adjuvant chemotherapy. When surgery is not possible, radiotherapy is the next choice. It is also possible to use radiofrequency ablation, cryoablation or photodynamic therapy [40].

In stage III cancers, radiotherapy and, in some cases, also immunotherapy are initiated before surgery is considered [40].

People with stage IV cancer are qualified mainly for systemic or palliative treatment. Immunotherapy is also applicable in these patients [40].

The choosing of the pharmacotherapy depends largely on the type of cancer and the expression of markers such as PD-L1, EGFR (epidermal growth factor receptor), BRAF (v-raf murine sarcoma viral oncogene homolog B), MET (MET proto-oncogene, receptor tyrosine kinase), ROS1 (ROS proto-oncogene 1, receptor tyrosine kinase), RET (ret proto-oncogene), NTRK (neurotrophic tyrosine receptor kinase) or ALK (anaplastic lymphoma kinase) [42–44].

Immunotherapy

One of the leading approaches to cancer treatment is immunotherapy. Unlike chemotherapy, which is based on causing cancer cells death or stopping cancer cells from dividing in a selected phase of the cell cycle by means of direct drug molecule interaction with the cell itself, the immunotherapy achieves its anti-cancer effect by stimulating the patient's immune system to respond to the tumor cells [45–48].

There are numerous approaches and methods to achieve this goal. They focus, for example, on the use of cytokines or their inhibitors, on the manipulation of signaling pathways involved in the activation process, apoptosis, lymphocyte exhaustion, and finally on the *ex vivo* production of anti-tumor lymphocytes [49, 50]. However, for the purposes of this study, which focuses on the role and position of durvalumab in lung cancer treatment, it is not necessary to discuss all of these methods in detail. Instead, the focus will be on discussing the PD-1–PD-L1 interaction and its role in the immune response to illustrate the effect of durvalumab.

"Immune synapse"

A junction called "immune synapse" is essential for the cellular immune system response, which is instrumental in combating cancer. It enables the CD8(+) T cell, the immune system cell responsible for the death of cancer cells, to "decide" whether to respond to a cell or not. Immune synapse is formed between the CD8(+) T cell and the body cell undergoing such control. Cells attach to one another using numerous signaling molecules present on their cell membranes. The most important of these connections is the connection between the T cell receptor (TCR) and the short peptide chain presented on the surface of the other cell by major histocompatibility complex class 1 (MHC1). Thus, similarly to antigen-antibody binding, the matching of the peptide to the TCR can be a stimulus to initiate a reaction. However, it is not the only signal that takes part in this process and is included in the immune synapse. There are numerous molecules that either promote or inhibit the initiation of a cellular response. Programmed cell death 1 (PD-1) is a molecule in the T cell membrane that binds to the programmed cell death ligand 1 on 2 (PD-L1 or PD-L2) on the second cell. This combination inhibits the immune response, which protects the cell verified by the lymphocyte. The above phenomena lead to the conclusion that the arrest of the PD-1–PD-L1 axis may promote the cellular response directed against the neoplastic cell. Thus, drugs are developed – antibodies, which aim to inhibit PD-1 or PD-L1 molecules [51–57]. One of the antibodies directed against PD-L1 inhibition is durvalumab.

Durvalumab

Currently, durvalumab is used both as monotherapy and in combination with other anti-cancer drugs. As monotherapy, the indications include treatment of locally advanced, unresectable non-small cell lung cancer in adult patients who express PD-L1 in ≥ 1% of tumor cells and who have not progressed after platinum-based chemotherapy. Durvalumab in combination with etoposide and carboplatin or cisplatin is indicated as the first line treatment of adults with extensive small cell lung cancer [58].

The efficacy of durvalumab in the above indications has been demonstrated in two randomized, multicentre clinical trials. For NSCLC and SCLC, these were the PACIFIC [59, 60] and CASPIAN [38, 39] studies, respectively.

PACIFIC study

PACIFIC is a double-blind, multicentre, randomized, placebo-controlled clinical trial. The study involved 713 patients with locally advanced, unresectable NSCLC. Patients had completed at least 2 cycles of radical platinum chemotherapy with radiotherapy within 1 to 42 days prior to study start and had an ECOG performance status (PS) of 0 or 1. Patients were randomized in a 2 : 1 ratio. They received durvalumab (n = 476) or placebo (n = 237) for up to 12 months or until unacceptable toxicity or confirmed disease progression. Randomization was stratified by gender, age (< 65 years or ≥ 65 years), and smoking status (smoking or non-smoking patient). Patients who were in remission at month 12th were offered re-treatment after disease progression. Assessment of responses was performed every 8 weeks for the first 12 months and every 12 weeks thereafter. From 63% of patients included in the study, it was possible to collect a sample allowing the assessment of PD-L1 expression in tumor cells. Two equivalent primary endpoints in the clinical trial were progression-free survival (PFS) and overall survival (OS) for durvalumab compared to placebo. The study demonstrated a statistically significant improvement in PFS in the durvalumab group compared to the placebo group (hazard ratio [HR] = 0.52 [95% CI: 0.42–0.65], p < 0.0001). A statistically significant increase in OS was also demonstrated in the durvalumab group compared to the placebo group (HR = 0.68 [95% CI: 0.53–0.87], p = 0.00251). In a 5-year follow-up analysis, with a median follow-up of 34.2 months, durvalumab continued

to improve OS and PFS compared to placebo. Improvement was achieved in all groups (regardless of gender, age and smoking status). However, no statistically significant efficacy was demonstrated in the group of patients whose PD-L1 expression was determined for < 1% of tumor cells [58–60].

CASPIAN study

The CASPIAN study was designed to assess the efficacy of durvalumab administered with or without tremelimumab in combination with etoposide and carboplatin or cisplatin. CASPIAN is a randomized, open-label, multicentre study in 805 treatment-naïve patients with extensive SCLC, a WHO/ECOG performance status (PS) of 0 or 1, body weight > 30 kg, eligible for platinum-based chemotherapy as first-line treatment, with a life expectancy ≥ 12 weeks, with at least one RECIST 1.1 target change and adequate organ and bone marrow function. The patients were divided into 3 groups. Group 1 received durvalumab, tremelimumab, etoposide, and carboplatin or cisplatin. Group 2 received durvalumab, etoposide and carboplatin or cisplatin. Group 3 received etoposide and carboplatin or cisplatin. The primary endpoint was the comparison of OS between groups 2 and 3, and between groups 1 and 3. When assessing the efficacy of durvalumab, the most important was the comparison of groups 2 (n = 268) and 3 (n = 269). The study showed a statistically significant improvement in OS in group 2 compared to group 3 (HR = 0.73 [95% CI: 0.591–0.909], p = 0.0047). Improvement was observed in all subgroups based on demographics, geographic region, carboplatin or cisplatin use, and disease characteristics [38, 39, 58].

MYSTIC study

The MYSTIC study [61, 62] compared the use of durvalumab (with or without tremelimumab) with the standard first-line therapy in the treatment of metastatic NSCLC. MYSTIC was an open-label, randomized study of 1,118 patients. As the primary endpoints, OS was compared between the durvalumab group and the standard therapy group, and the OS and PFS were compared between the durvalumab and tremelimumab group, and the standard therapy group. Groups were randomized 1 : 1 : 1 and primary endpoints (OS and PFS) were assessed in patients expressing PD-L1 on ≥ 25% of tumor cells. No statistically significant relationship was observed in any of the specified endpoints.

Drug safety

In the PACIFIC study, pneumonia or radiation pneumonitis were observed more frequently in the durvalumab group (33.9%) than in the placebo group (24.8%). Other immune-related inflammations of the liver, colon, pituitary, kidney, heart muscle, meninges, brain, bladder and pancreas have also been observed in patients receiving durvalumab. In addition, there were disturbances in endocrine function of thyroid, adrenals, pituitary and pancreas. Rash, myasthenia gravis, polymyositis, Guillain-Barré syndrome and thrombocytopenia were also observed. There have also been reports of serious infusion-related reactions [58–60].

CONCLUSIONS

The above study brings together the current knowledge on lung cancer and the use of durvalumab in its treatment. Currently, durvalumab plays an important role in the treatment of both small cell and non-small cell lung cancer. In parallel with immunotherapy, numerous novel therapies arise. The goal of modern treatment development is an individual approach based on the molecular pattern of the cancer. The ongoing clinical trials focus on various biological targets including [63, 64]:

- the inhibition of the DNA damage repair – with a special role of poly adenosine diphosphate-ribose polymerase (PARP) inhibitors [64–68]
- the role of cell cycle checkpoints responsible for arresting the cell cycle in order to repair the damaged DNA [68, 69]
- the reactivation of the blocked apoptotic pathways [70]
- the inhibition of the dysregulated transcription – and related modifications of the epigenetic mechanisms [71–75]
- targeting the tumor vasculature [76, 77].

As emphasized above, the development of modern treatment methods such as immunotherapy with durvalumab is crucial to taking the next strides in the difficult struggle against the leading cause of cancer-related death in the world.

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