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Immune checkpoint inhibitors in non-small cell lung cancer — towards daily practice

Abstract

Immunotherapy with immune checkpoint inhibitors (ICIs) revolutionized therapy of solid tumors, among them- lung cancer. PD-1, PD-L1 blockers have been shown to improve overall survival in advanced, metastatic non-small cell lung cancer. In individual patients, 3-5-year survival has been achieved. Nivolumab, pembrolizumab, atezolizumab are approved in lung cancer treatment. Practical observations in real life show that the results are comparable with those achieved in clinical trials. The effects of ICIs depend on the patient performance status; age, sex, histology; the presence of brain metastases have not modified treatment results. ICIs therapy is safe and well tolerated; immune related adverse events are observed. Pneumonitis may be a serious and fatal complication, but glucocorticoids are usually curative. For proper patients selection for ICIs treatment, the detection of PD-L1 expression on cancer cells is used. The so-called "hot" tumors with high expression of PD-L1 and abundant infiltration by cytotoxic cells seem to better respond to treatment than "cold" tumors.

Key words: lung cancer, PD-1, PD-L1, immunotherapy, adverse events, immunoscore

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Introduction

Four years ago we paved a new direction in lung cancer treatment in this Journal [1]. Thereafter immunotherapy with checkpoint inhibitors in lung cancer became a fact. As about 70% of non-small cell lung cancers at the moment of recognition are in advanced stages of the disease, immunotherapy with checkpoint inhibitors may be a better chance than chemotherapy for patients at advanced stage of cancer. The new WHO 2015 histological classification is adjusted to the newest most effective treatment regimens. The methods of the classification allow to distinguish the main types of NSCLC with high accuracy (Table 1) [2]. Whereas the latest 8th clinical categorization reflects important progress in the methods of precise evaluation of primary tumor, tumor spread and metastases [3].

Furthermore, the precise molecular biology methods help in the proper selection of patients for a targeted therapy with tyrosine kinase inhibitors (TKI) [4]. On the grounds of the accurate

diagnosis with an individual cancer characteristic, the immunotherapy raises the new hopes for patients and seems to significantly change the perspectives in lung cancer. The aim of this short review is to present the current reports of the use of checkpoint blockers in daily clinical practice beyond the conditions of clinical trials.

From clinical trials

Natural anticancer defence in the host organism is known as immunosurveillance, in which the cytotoxic reaction directed to the cancer cells is capable of inducing their apoptosis and death. The main cytotoxic cells are CD8+ lymphocytes. Natural killer cells (NK), natural killer T cells (NKT), CD4+ lymphocytes complement this cytotoxic cell population. An anticancer reaction in the tumor environment (TME) is supported by Th1 cytokines (IL-2, INF- γ , TNF- α) and M1 macrophages. However, the mechanisms of suppression and regulation of immune response cause the escape of cancer from immunosurveillance

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Table 1. Accurate histological diagnosis is crucial for therapeutic decision in lung cancer. The WHO classification of non-small cell lung cancer; a proper diagnosis based on immunohistochemistry SCC: squamous cell carcinoma; LCC: large cell carcinoma; NOS: non-otherwise specified

Immunohistochemistry			Diagnosis	
TTF1	p40	CK 5/6	Surgical biopsy resection	Small biopsy, cytology
+	±	±	Adenocarcinoma	NSCLC favour adenocarcinoma
–	+ (diffuse)		SCC	NSCLC favour SCC
–	+ (focally, <10% of cells)		LCC unclear	NOS
–	–	–	LCC null	NOS
no stains available	no stains available	no stains available	LCC with no additional stains	NOS (no stains available)

along with cancer development. This process is complex and it includes the participation of many regulatory cells and mediators. The suppressive molecules, which are overexpressed on/in lymphocytes in the cancer milieu, play a role in immunosuppression [1, 5–7]. The issue of suppressive molecule function is to form an inhibitory pathway by connection with the corresponding ligand on a cancer cell. Such a pathway avoids the activation of cytotoxic effector lymphocyte and causes its anergy and immunosuppression. A classic example of the inhibitory signalling pathway is the programmed death-1 (PD-1)/programmed death-1 ligand 1 (PD-L1) pathway.

PD-1 molecule and its inhibitory function was discovered by Ishida and Honjo in the 90's of the twentieth century. PD-1 receptor is expressed on T cells, B-cells, NK-cells and regulatory T cells. In our studies, we found a higher expression of PD-1 on memory and activated T cells than on naïve cells in lung cancer TME on the basis of bronchoalveolar lavage fluid (BALF) examination. The proportion of PD-1 positive cells was higher in the BALF from the lung affected by cancer than in the opposite, “healthy” lung and from peripheral blood (I. Kwicien, ERS Congress, 2017). The ligands to PD-1: PD-L1, PD-L2 are expressed on malignant tumor cells, antigen presenting cells and other immune cells. The overexpression of PD-1 on lymphocytes and PD-L1, 2 on cancer cells is observed in many malignancies, and in lung cancer as well. The suppressory molecules are

known as “checkpoints”. The nature of currently applied cancer immunotherapy is inhibition, blockade of these checkpoints by so-called “immune checkpoints inhibitors” (ICIs). ICIs were approved to date in melanoma, squamous cell carcinoma of the head and neck, Hodgkin lymphoma, kidney carcinoma, Merkel cell carcinoma, colon and ventricular carcinoma [8].

Anti-PD-1 inhibitors: nivolumab and pembrolizumab, anti PD-L1 inhibitor- atezolizumab are approved in non-small cell lung cancer (NSCLC) therapy. In clinical trials: Check Mate 017, Check Mate 057, Keynote 010 and OAK, respectively, these agents have shown improvement of overall survival when compared with docetaxel chemotherapy in second line therapy of advanced NSCLC [9, 10]. In the first line setting, the pembrolizumab was shown to improve the response, while nivolumab was not. Anti-PD-L1 antibody durvalumab in the ATLANTIC and PACIFIC studies in third line setting was more effective than docetaxel. To date the only predictive factor for ICIs in lung cancer is the expression of PD-L1 on tumor cells. A threshold for PD-L1 expression in trials was defined as: 1–5–10% PD-L1 positive cancer cells. At least 50% of them were shown to be predictive of pembrolizumab when compared with docetaxel in the first line setting of treatment. In the OAK study with atezolizumab, PD-L1 expression on the tumor cells and also on immune cells was taken into account. In spite of the fact that in the majority of studies PD-L1 expression was assessed, the methodological discussion concerning immunohistochemical detection of PD-L1 has not ended [9, 11].

After trials

One could say that ICIs revolutionized advanced lung cancer therapy. The most striking is an achievement of prolonged survival of some patients with advanced, metastatic disease. In clinical trials (CheckMate, Keynote, OAK), the median overall survival (OS) was prolonged from 9.2 to 13.8 months [10]. Taking into account the results of clinical studies, immunotherapy has recently been introduced in the first line and second line setting in advanced NSCLC, as presented in Figure 1. Nivolumab and pembrolizumab are humanized anti PD-1 antibodies class IgG4. Pembrolizumab could be used in the first line of treatment, in NSCLC patients with PD-L1 expression on more than 50% of tumor cells. However, pembrolizumab in second line treatment is used in patients with any expression of PD-L1 on tumor

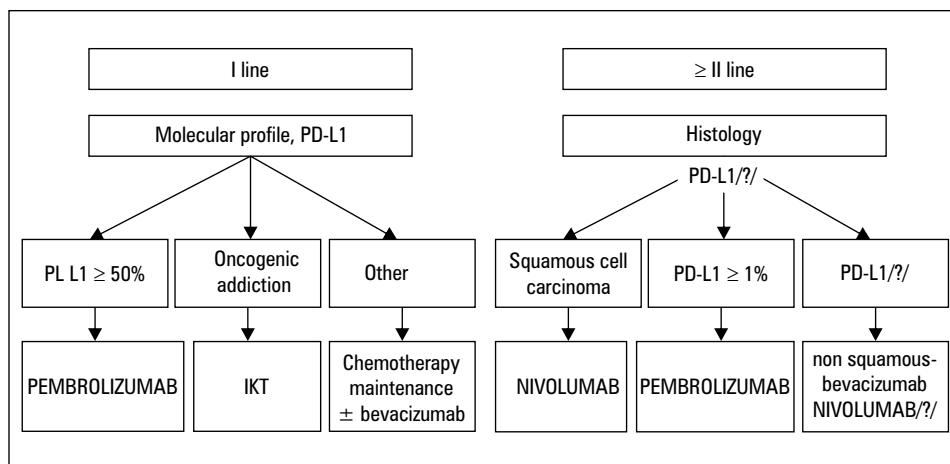


Figure 1. First and second line treatment regiments proposal in advanced non-small cell lung cancer: a place for immunotherapy with immune checkpoints inhibitors (presented by Cardanel J, *Congres de Pneumologie de Langue Francaise*, 2018). IKT: tyrosine kinase inhibitors, PD-L1: programmed death ligand 1

cells (more than 1% of tumor cells). Pembrolizumab is used at a constant dose of 200 mg every 3 weeks. The recommended dosage of nivolumab is 3mg/kg, IV, every 3 weeks. Atezolizumab is anti PD-L1 antibody, administered 1200 mg, IV, every 3 weeks [4, 12]. Recently the first reports from after-trial observations of the use of ICIs in clinical practice have been made available.

Dudnik *et al.* [13] present their study conducted in Israel among 342 consecutive patients with advanced lung cancer (stage IV), also those in poor performance status, treated with nivolumab. A median follow-up was 18.5 months. Unfortunately, 60% of the subjects died. The median OS was 5.9 months. Of all parameters analyzed: age, sex, smoking history, tumor histology, brain metastases, previous treatment, only performance status (PS) has been shown to have influence on response to the treatment. In the patients with ECOG PS 0–1, the median OS achieved was 9.5, vs. the patients with PS ≥ 2, in whom median OS was 3.5 months. The treatment was safe, 1–2 grade pneumonitis was found in 3 patients, and grade 3–4 in 1 patient. The authors concluded that in reality, the effectiveness of nivolumab was less prominent than in the clinical trials. The OS was related to the patient status: the better the PS the longer the OS (real life). CLINIVO was a multicentre French study. The goal of CLINIVO was to evaluate the results of nivolumab treatment in a real-life setting [14]. 900 patients with stage IIIB/IV cancer were included and observed with a median follow-up of 26.1 months. The results were comparable with those achieved in the clinical trials. The median OS was 10 months, adverse events were observed in 12% of pa-

tients. Also in this study, there were patients with 24-month survival. The presence of brain and liver metastases and poor PS were shown to be significant unfavorable agents of response to nivolumab. The other study was CheckMate 153, the first randomized study to evaluate treatment duration with a PD-1/PD-L1 inhibitor presented by D.R. Spigel on Congress European Society for Medical Oncology (ESMO) 2017. The prevalence of continuation of treatment after 1 y vs. discontinuation and retreatment was noted by the authors. Individual 2-year survival was achieved in some patients. In Italian observation presented by F. Grossi on ESMO Congress 2017, an expanded access program of 1588 patients in nivolumab treatment was evaluated. The median OS was 11 months, 48% of patients survived one year, about 40% — 18 months. The safety of nivolumab was confirmed, pneumonitis was observed in 1–2% of the treated. A study currently conducted in France includes 10 000 patients with advanced NSCLC qualified to second line setting treatment with ICIs. To date the mean OS was 8 months, 39% of the treated survived 6 months, 12% — 12 months [14]. It was presented in many studies and in some subgroups of clinical trials that patients with oncological addiction (*EGFR* mutations, *ALK*, *ROS1* rearrangements) benefit little from PD-1, PD-L1 blockers therapy [9, 15]. *KRAS* mutation and mutation in 14 exon of *MET* gene are connected with a response to ICIs treatment in observation of single patients [16].

To summarize, real-life observations present that ICIs in lung cancer are efficient to a similar extend as in trials, and the answer is highly in-

dividual. In these observations patients age, sex, presence of brain metastases, tumor histology and smoking history have not impacted treatment efficacy. In qualification to ICIs therapy, the patient's PS should be included.

Safety

As checkpoint blockade activates the immune system, the adverse events (AEs) related with disordered immunity could be expected. These are so-called "immune-related AEs" (ir AEs). Their pathomechanism is connected with autoimmunity. Interestingly, only some selected organs are affected, independently of the type of primary tumor. The mostly affected organs are as follows: gastrointestinal tract, thyroid, lung, skin, liver with the signs of: thyroiditis, colitis, pneumonitis, brain inflammation [17, 18]. The irAEs are observed in patients treated with anti CTLA-4 as well as with anti PD-1 blockers, but pneumonitis and thyroiditis are more common in the latter group. For PD-L1 blockers, similar autoimmune disorders are observed as for PD-1 inhibitors. The incidence of irAEs in patients receiving PD-1, PD-L1 blockers was 10 to 16%. The mechanism of immune AEs is not fully understood, it is rather connected with autoantibodies than with a cellular response. The reasons for an individual tendency to immune-related AEs are unknown; the role of the host's microbiota is taken into account. Real-life observations show that a pre-existing nonactive autoimmune disease is not a risk factor for irAEs. In a recently presented report of three cases with idiopathic pulmonary fibrosis (IPF) treated with nivolumab, nonworsening was observed [19].

IrAE severity is graded from 1 to 5 (the most severe). Immunosuppression with glucocorticoids was shown to be effective in treatment of irAEs. IrAEs occur early, even after the first doses of medication. The risk of AEs does not cumulate with doses of blockers or prolonged treatment. Thus, in an individual patient, a therapy may be continued for years. To date there are no data that the AEs are related to the efficacy of checkpoint blockers [18]. According to a recent statement of the American Society of Clinical Oncology (ASCO), it is recommended to:

- in the case of grade 1 irAEs: the continuation of immunotherapy with careful monitoring,
- in grade 2 irAEs: an initial dose of prednisone 0.5 or 1 mg/kg/d.,
- for grade 3: prednisone in the dose of 1–2 mg/kg/d. or methylprednisolone IV or, if no improvement — infliximab; if after the therapy

symptoms of irAEs revert to 1 grade, the ICIs treatment may be continued',

- for grade 4 irAEs: the discontinuation of immunotherapy [17].

Education about an early recognition of irAEs is the key to successful treatment. It is pointed out that the patients, their family, nurses, pharmacists, frontline physicians, all should be committed to a proper diagnosis of irAEs [17]. There are online projects enabling the reporting of all irAEs to the dedicated databases, e.g., the one run by the European Respiratory Society (ERS).

Pneumonitis is a special kind of irAE needing caution in the case of lung cancer ICIs therapy. This non-infectious immune disorder resembling interstitial lung disease may be serious. Almost all kinds of features of interstitial lung diseases (ILD) were described in the CT scans of patients with past ICIs pneumonitis [20]. The new changes on a chest X-ray or CT scan in the patient treated with PD-1, PD-L1 blockers need special attention. The following reasons for these changes are possible: progression of the disease, infection, pneumonia, radiation effects if the patient was previously treated with an rtg therapy, and pneumonitis. The incidence of pneumonitis is relatively low (2.7% in metaanalysis of 20 studies (17) but may be serious. In the Keynote 001 study with pembrolizumab 2-10 mg/kg IV, pneumonitis was observed in 3.8% of the patients, in half of them in grade 3–5 [21]. In the OAK study with atezolizumab, pneumonitis was noted in 1% of patients [22]. In French real-life studies, pneumonitis was not frequent, i.e., 1–2%. A higher incidence of this complication was described in a combined therapy: nivolumab + ipilimumab.

How to select patients for ICIs?

What about biomarkers? To date, the only predictive factor for the ICIs therapy seems to be a proportion of cancer cells with the detected expression of PD-L1. For pembrolizumab, the OS was found to be longer when the tumor proportion score (TPS), i.e., the proportion of PD-L1 positive cancer cells was high. The higher the proportion of PD-L1 positive cells the better the median survival. For nivolumab and atezolizumab, the collected data were less convincing. In clinical trials, different immunohistochemistry (IHC) tests for evaluation of PD-L1 expression were used showing conflicting results. Thus, currently, the efforts are made to find the most accurate antibody anti PD-L1 for IHC, the best detection system, digitalized methods of cell counting and

well-trained staff [21, 23]. Some studies are conducted to develop a proper assessment scheme. In practice, PD-L1 expression should be evaluated when a pembrolizumab treatment is planned. It is recommended to use only histological paraffin-embedded samples from a large tumor biopsy, metastases or archival material; cytological material is not acceptable [9]. The main reason for pitfalls is the cancer tissue heterogeneity. For certain quantitative evaluation of PD-L1 expression, the availability of a large fragment of cancer tissue is required. Whereas in practice, the resection rate in NSCLC is below 25%, the immunotherapy is restricted to the advanced stages of cancer and the tendency to less invasive procedures, as a small needle biopsy in lung cancer diagnosing dominates. It causes the lack of good quality samples for tumor tissue characteristic. The same remark concerns the examination of inflammatory infiltration in TME, especially tumor infiltrating lymphocytes (TIL). There is evidence that evaluation of the character of immune response in the cancer site, the so-called "immunoscore" [24, 25], may be crucial for the proper patients selection and prediction of irAEs, especially in the lung. We have presented in many studies the role of analysis of bronchoalveolar lavage fluid from the lung affected by cancer in assessing local immunity [25–29]. What is more, the lungs are extremely affected by harmful factors like tobacco smoke, pollutants, aging, other chronic diseases (COPD, ILD), treatment (antibiotics, immunosuppressive agents, previous anticancer treatment, hypoxia, microbiota). The influence of all the above agents may be detected in BALF.

Apart from individual patients' features and the character of cancer, the resistance to ICIs may cause a treatment failure [30]. The issue of PD-1/PD-L1 blockers is the inhibition of the negative regulatory function of PD-1/PD-L1 pathways resulting in restoring the primary antitumor immune response. This response to ICIs is highly individual; beside those with good results of treatment, there are patients who do not respond to the initial therapy, who partly respond or who acquire resistance to ICIs. The understanding of the mechanisms of this primary or acquired resistance is important in the context of finding biomarkers for immunotherapy. If we want to restore the anticancer function of the immune system, the latter should work properly. For the success of ICIs therapy, an appropriate population of T cytotoxic cells is required. The presence of CD8+ lymphocytes (cytotoxic T lymphocytes, CTLs) was found to be a predictive factor in im-

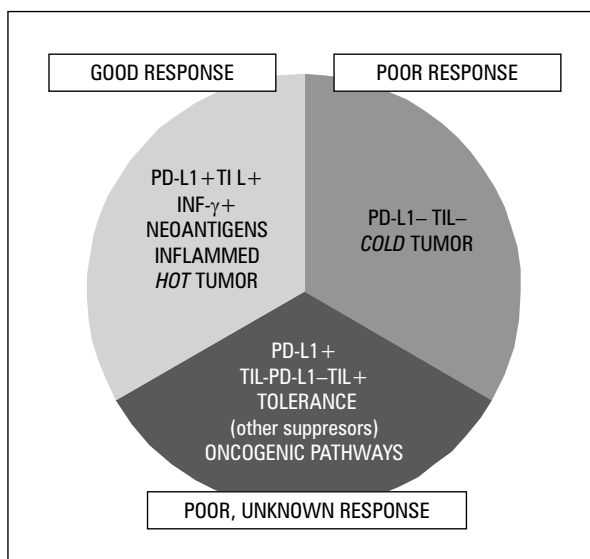


Figure 2. Types of tumor microenvironment in the context of efficacy of immunotherapy with immune checkpoint inhibitors; TIL: tumor infiltrating lymphocytes; INF: interferon

munotherapy in many studies [10, 30]. Resistance to ICIs may be caused by insufficient activity of CTLs or disrupted antigen presenting cells function. The deletion of CTLs in malignancy is observed and is a common reason for resistance to ICIs. The other mechanism is the lack of PD-1 stimulators, like INF- γ . Tumors with molecular alterations: EGFR mutation, ALK rearrangements are found to be resistant to ICIs. Finally, many mechanisms of immunosuppression and regulation work together in TME, the PD-1/PD-L1 axis is not isolated. Regulatory T cells, myeloid derived suppressor cells (MDSCs), regulatory B cells, M2, immunosuppressory cytokines and suppressory molecules on T cells contribute to silencing the immune reaction in TME [6, 7].

In the studies of the role of immunoscore in providing the answer to ICIs, the division of the tumors to "hot" and "cold" became accepted. The "hot" tumors represent those with the best response to ICIs (Fig. 2) [31]. These are tumors with high mutation burden (TMB), releasing new neoantigens and more susceptible to ICIs than the more stable cancers (among others observed in smokers). Improved high-throughput technologies are providing feasible tools for analyzing the mutation antigen profile, the gene signature and epigenetic modification of tumor and immune cells, the breadth of antibody responses, as well as the magnitude, homing capacity, cytotoxic function and T cell receptor (TCR) repertoire of T lymphocytes. The following novel technologies are incorporated into research: whole

Table 2. Activating and suppressory molecules on a T lymphocyte and its ligands on a cancer cell — possible targets for immunotherapy in lung cancer

Immune Checkpoint receptors		
Tumor cell	Tcell	Function
ICOS-L	ICOS	Activation
MHCclass1/11	KIRs	
OX-40L	OX-40	
GITR-L	GITR	
CD80	CD28	
CD86	CD28	Inhibition
CD80	CTLA-4	
CD86	CTLA-4	
PD-L1	PD-1	
PD-L2	PD-1	
Gal-9	TIM-3	
VHEM	BTLA	
	VISTA	

exome sequencing for neoantigens discovery, gene signature and pattern, epigenetic-differentiation-based immune cell quantification, protein microarray (seromics), T and B cell receptor deep sequencing [32].

Perspectives

There is a growing body of evidence that classical therapies such as chemotherapy, radiotherapy, stereotactic ablative therapy are capable of improving the results of ICIs [34]. Combined regimens are widely investigated [9, 33]. The promising results of combined therapy of nivolumab with CTLA-4 antibody-ipilimumab have been shown [35]. In the near future immunotherapy may be helpful in an early stage of disease; III phase of clinical trial with anti-PDL1 antibody-durvalumab is ongoing [9]. Finally, there are much more pathways beyond PD-1/PD-L1 in cancer, which are possible targets for modification (Tab. II) [36]. The treatment of lung cancer has entered a new era.

Conflict of interest

The author declares no conflict of interest.

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