IMMUNOTOXICITY OF PEMBROLIZUMAB IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER: A SINGLE-CENTRE STUDY

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ABSTRACT

Background: *Immunotherapy represents a new form of treatment that stimulates the immune system to destroy cancer cells. Pembrolizumab is a humanized monoclonal antibody that binds to the PD-1 programmed cell death receptor and blocks its interaction with the PD-L1 and PD-L2 ligands. The aim of this study was to determine the efficacy and safety of the pembrolizumab drug, in the first line of treatment in patients with metastatic non-small cell lung cancer (NSCLC).*

Methods: *The research was retrospective and was conducted at the Institute for Pulmonary Diseases of Vojvodina (IPDV). It included patients treated in the period from January 2018 to December 2019, in whom metastatic NSCLC was verified.*

Results: *The study included a total of 20 patients - 10 men and 10 women. The average age was 61.75 years. The average length of therapy was 15 cycles (45 weeks), the minimum was 1, and the maximum was 33. Twelve patients (60%) had a lethal outcome. The median time to disease progression was 8.1 months and the overall survival was 14.6 months. Of the total number of patients, 13 (65%) had side effects to immunotherapy, and 7 (35%) did not experience any. Out of a total of 13 patients who had side effects, 9 had only one isolated, 4 had more associated side effects, of which 3 patients had 2 associated, and 1 patient had 3 associated side effects.*

Conclusion: *Based on the results, immunotherapy certainly occupies an important place in the treatment of metastatic NSCLC. Namely, the lack of severe side effects linked to cytotoxic chemotherapy and the relative ease of treating immune related adverse events (irAEs) that occur with immunotherapy, good overall survival and later onset of disease progression opens the door to the possibility of a better quality of life for these patients and the prolongation of their lifespan.*

Key words: *NSCLC; First line treatment; Immunotherapy; irAEs*

INTRODUCTION

The most recent global report on the epidemiology of neoplastic disease states that lung cancer has the highest mortality among 36 cancer types considered, and it is the second most frequently diagnosed cancer type in the world. Around 85% of all lung cancer is classified as non-small cell lung cancer (NSCLC) (1,2).

The mortality is associated with a high degree of malignancy and late diagnosis. As many as 65.33% of men diagnosed with lung cancer are at the advanced local stage (stage III) or with present distant metastases (stage IV) (2,3).

In the last decade, significant progress has been made in the treatment of lung cancer with the introduction of targeted biological drugs and more recently immunotherapy (4). Cancer cells have multiple immunosuppressive mechanisms to escape from the immunological response and survive. Therefore, immunotherapy exploits the concept of activating or regulating the immune system to identify and kill cancer cells (5).

To date, one of the main approaches is to develop immune checkpoint inhibitors (ICI) that will target pathways used by cancer cells to escape the immune system.

So far, one mechanism of the immune escape changing paradigm in the management of metastatic NSCLC is through the modulation of immune checkpoints, including cytotoxic T-lymphocyte antigen 4 (CTLA-4) and the axis PD-1/PD-L1, which regulate the priming phase and effector phase of T-cell activation (6). Monoclonal antibody therapies targeting the interaction between PD-1 and its ligands, PD-L1 and PD-L2, have shown remarkable efficacy in treating and curing cancer (Figure 1) (7).

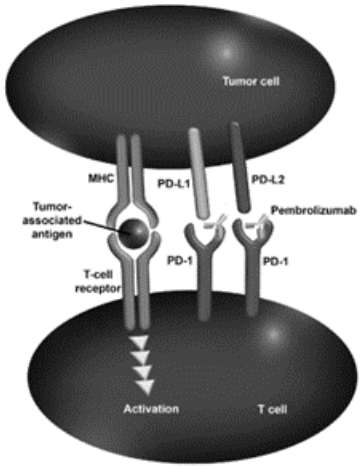

Figure 1. Mechanism of action of the anti-PD-1 antibody pembrolizumab.

One such drug is pembrolizumab, a humanized monoclonal anti-PD-1 antibody that is used in the treatment of various cancers such as melanoma, Hodgkin's lymphoma, bladder cancer, head and neck squamous cell cancer, and as of year 2015, first FDA approved ICI in the treatment of NSCLC (8).

Most of the ICIs proved a limited benefit with 10%–20% overall response rates of monotherapy. One of the approaches to improve the ICIs efficiency consists in the development of better predictive biomarkers. Another approach is the combination treatment strategies such as ICI combinations with chemotherapy, radiotherapy, or tyrosine kinase inhibitors (TKI) (9-11).

In combination with pemetrexed and platinum-containing chemotherapy, it is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumors are negative for EGFR or ALK gene mutations. Pembrolizumab, as monotherapy, is indicated for the treatment of metastatic NSCLC in adults whose tumors express PD-L1 with TPS ≥50% and who are not positive for tumor mutations of the EGFR or ALK genes. PD-1 inhibitors can block the negative regulatory signals of T cells to terminate immune suppression and enhance the anti-tumor effect of T cells. However, this mechanism may also excessively activate T cells, which leads to an imbalance of immune tolerance and performs an autoimmune-like inflammatory response called immune-related adverse events (irAEs) when it affects normal tissues including the skin, digestive tract, liver, endocrine gland, lungs, and so on.

Due to the increasing use of ICIs, and the wide range of possible adverse reactions, the American Society of Clinical Oncology (ASCO) has introduced guidelines for the treatment of irAEs. Most of the irAEs that occur during the treatment of patients with pembrolizumab are reversible, so they are managed by temporarily stopping the treatment with pembrolizumab, using corticosteroids and/or supportive therapy (12,13). Depending on the severity of the adverse reaction, it is necessary to delay the administration of pembrolizumab and administer corticosteroids. After the improvement to ≤ grade 1, the dose of corticosteroids should be gradually reduced and continued for at least 1 month. Pembrolizumab may be reintroduced within 12 weeks of the last dose if the adverse reaction remains ≤ grade 1 and the corticosteroid dose is reduced to ≤10 mg of prednisone or the equivalent per day. Pembrolizumab treatment must be permanently discontinued in the event of the recurrence of any grade 3 irAE and in the event of any immune-related grade 4 toxic adverse reaction, except for endocrinopathies that can be controlled by hormone replacement. In the case of immunologically caused endocrinopathies, long-term hormone replacement therapy may be required (14).

The aim of this study was to present the results regarding the incidence and severity of irAEs of pembrlizumab used in a group of patients treated for NSCLC at one centre in a limited time period.

METHODS

The research was retrospective in nature and was conducted at the Institute of Pulmonary Diseases of Vojvodina (IPBV), in the Pulmonary Oncology Department, and included patients treated between January 2018 and December 2019 who were diagnosed with metastatic NSCLC. All patients were treated with the first line of immunotherapy, i.e. the checkpoint inhibitor, pembrolizumab (Keytruda®). This was a pilot study and at the time only a small number of patients met the needed criteria.

The drug pembrolizumab, as monotherapy, is indicated as the first-line treatment of metastatic NSCLC in adult patients whose tumors express PD-L1 with a TPS ≥50% (tumor proportion score - TPS), and who are not positive for tumor mutations of the EGFR or ALK genes, which was also the criteria for selecting patients for treatment.

The drug pembrolizumab was administered by intravenous infusion at a dose of 200 mg per day for 30 minutes, every 3 weeks until the onset of disease progression.

All the used data on respondents were obtained from the IPBV database.

The data related to the patients sex, age, comorbidities, histological type of cancer, localization of cancer, number and localization of distant metastases, type, grade and therapy of irAEs, number of cycles of therapy until the appearance of irAEs, total number of cycles of therapy received, progression-free survival time, and overall survival was collected and processed.

The collected data was further entered into a Microsoft Excel spreadsheet. After that, the statistical processing of the data was done, and the results were presented in tables and graphs with textual comments.

RESULTS

The study included a total of 20 patients, of which there were 10 men (50%) and 10 women (50%). The average age was 61.75 years, ranging from 35 to 81 years, with the highest number of patients in the age range of 60-69 years.

Of the total number of patients, 7 (35%) had no associated diseases, while 13 (65%) patients had comorbidities. The largest number of patients, 11 (85%), had comorbidity in the form of cardiovascular diseases (CVD) such as hypertension, heart rhythm disorders, chronic heart failure, 5 (38%) of them had chronic obstructive pulmonary disease (COPD), and 3 (23%) of the patients had diabetes mellitus (DM) as an associated disease. Four patients had combined comorbidities, CVD with COPD, and 2 had CVD with DM (Table 1).

Table 1. Patients age and comorbidities.

Age range	Sex		Total	Type of comorbidity	Total
	M	W			
30-39	1		1	Cardiovascular disease	11
40-49		2	2	Chronic obstructive pulmonary disease	5
50-59	1	3	4	Diabetes mellitus	3
60-69	5	3	8	CVD + COPD	4
70-79	2	2	4	CVD + DM	2
80-89	1		1		
Total	10	10	20		

Given that only patients with NSCLC were included in the research, of the total number of patients, 16 (80%) had proven adenocarcinoma, and 4 (20%) had proven squamous lung cancer. Regarding the location of the cancer, of the total number of patients, in 11 (55%) the tumor was localized in the right upper lobe, in 6 (30%) in the left upper lobe, in 2 (10%) in the right lower lobe and in 1 (5 %) it was localized in the left lower lobe. All patients had metastatic NSCLC (stage IV), with 17 (85%) patients having multiple metastases, and only 3 (15%) having a solitary metastasis. In 12 (60%), only one organ was affected by metastasis, in 8 (40%) patients, one or more organs were affected by metastasis, and of those eight patients, two had as many as three organs affected by metastases. The most common localization of metastasis was the lungs, as many as 8 (27%) times, then the bones 6 times (20%), then the liver and adrenal gland, which were the site of cancer metastasis 4 (13%) times, the CNS 3 times (10%), pleura and retroperitoneal space 2 (7%) times each and the skin only 1 (3%) time. (Chart 1).

On average, the length of therapy administration was 15 cycles (45 weeks), the minimum was 1 cycle, and the maximum was 33 cycles of therapy. The duration of therapy was until the onset of disease progression. Of the total number of patients, 12 (60%) had a fatal outcome.

The average time for disease progression from the moment of starting pembrolizumab therapy was 8.1 months, and the overall survival was 14.6 months. The accuracy of these data must be viewed with the knowledge that 5 patients were still on pembrolizumab therapy, and three had received other types of therapy due to disease progression (chemo and radiotherapy) at the time of writing this paper.

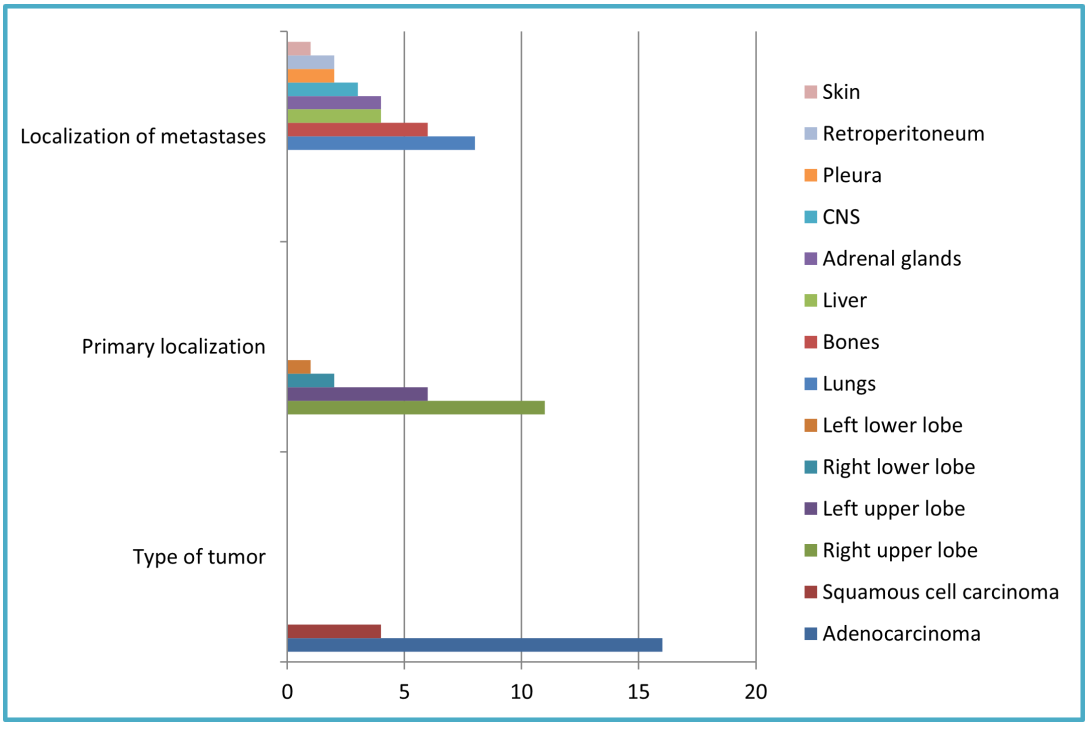

Chart 1. Tumor characteristics among our patients.

Out of the total number of patients, 13 (65%) had adverse events (AEs) after pembrolizumab therapy, and 7 (35%) did not. Of those 13 patients who had AE due to the received therapy, 9 had only one isolated AE, while 4 had multiple associated AEs, of which 3 patients had 2 associated AEs, and 1 had 3 associated AEs. Thus, there were a total of 18 registered AEs.

On average, it took 7 cycles of therapy (21st week) until the onset of AE. The shortest time for which AE occurred was after 1 cycle (3rd week), and the longest time elapsed until the onset of AE was 18 cycles (54th week).

Of the irAEs that were reported during the research, there were no grade IV or V irAEs, four patients reported grade I, ten reported grade II, and four reported grade III. Grade I, apart from monitoring the patient's condition, did not require any additional intervention, while grades II and III were, in accordance with recommendations, cured with adequate therapy. The toxicity rates are in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v.5) (Table 2.).

Table 2. Grade and frequency of AEs.

Adverse Event	Sex					Total	Therapy for AE	
	I	II	III	IV	V		With	Without
Thyrotoxicity	2	5	0	0	0	7	5	2
Pneumonitis	0	2	1	0	0	3	3	0
Enterocolitis	1	0	1	0	0	2	1	1
Hematological toxicity	0	1	1	0	0	2	2	0
Gastritis	1	0	0	0	0	1	0	1
Skin changes	0	1	0	0	0	1	1	0
Pericarditis	0	1	1	0	0	2	2	0
Total	4	10	4	0	0	18	14	4

Thyrotoxicity was the most frequent adverse event of the received therapy, occurring in 7 (39%) patients, of which 5 required substitution therapy (grade II), and 2 patients did not need any therapy (grade I).

Pneumonitis occurred in 3 (17%) patients, 2 were grade II and one was grade III AE, all of which required drug discontinuation and recommended corticosteroid therapy.

Enterocolitis occurred in 2 (11%) patients, in one it was grade I and did not require any treatment, while in the other one it was grade III and was treated in the hospital.

Hematological toxicity occurred in 2 (11%) patients, grade II and III, as therapy iron (grade II) and transfusion of blood products (grade III) were given.

Gastritis occurred in 1 (5.5%) patient and did not require any therapy (grade I).

Skin changes also occurred in 1 (5.5%) patient and required the use of corticosteroids (grade II).

Pericarditis occurred in 2 (11%) patients, as grade II and grade III, which were treated with corticosteroids and drainage of the pericardial effusion (grade III).

DISCUSSION

It is well known that in terms of annual morbidity and mortality, lung cancer ranks first in the whole world, including our country, of all malignancies and in both sexes and all age categories, which is confirmed by the epidemiological data of the International Agency for Research on Cancer. What is particularly worrisome is the increasing equalization of the incidence of lung cancer between the sexes and the lowering of the age limit for its detection, which the data from GLOBOCAN and our research confirmed. (1,2).

Among the histological subtypes of NSCLC, adenocarcinoma is more often represented than squamous carcinoma and is often accompanied by comorbidities from the cardiovascular and respiratory system, well-known risk factors for this disease, which is proven by numerous world studies and authors (2,3).

Given that our research included only patients with stage IV NSCLC, which meant that the disease had spread to other organs, the number and arrangement of metastases was not surprising, but their localization greatly affected the further course of the disease, its outcome and accompanying therapy, resulting in a certain number of patients that had to stop pembrolizumab therapy due to the disease progression and consequent palliative radiation of metastatic changes and switch to chemotherapy.

Unfortunately, NSCLC is usually diagnosed at later stages (IIIB and IV, as much as 40%), accompanied by a very low percentage of five-year survival (<10%) (statistics based on 7 countries (EU 5, USA and Japan)), meaning that the therapeutic choices at this stage are far more limited and often reduced to the alleviation of symptoms by the tumor itself and metastatic changes, thus our results regarding the average overall survival (14.6 months) and the time elapsed until the disease progression (8.1 months) were not surprising.

Out of all of our patients, not one requiered permanent discontinuation of their treatment with pembrolizumab. Only four of them (3 patients with pneumonitis, and 1 with enterocolitis treated in the hospital) were treated with corticosteroids following a temporary break in immunotherapy. Among our patients, the most reported irAEs was thyreotoxicity (7 patients or 39%), which is the most common pembrolizumab-mediated endo-

crine toxicity, leading to grade 1 or 2 hypothyroidism (4–8%), hyperthyroidism (2–5%), and rare acute thyroiditis (<1%). Luckily, in the case of our patients, 5 of them only required hormon supstitution therapy.

In concordance with the KEYNOTE study, skin toxicity proved to be the most common irAEs associated with pembrolizumab, but since our results were limited to a small number of patients, it was reported in only 1 (grade II) and was treated with corticosteroid therapy.

Fortunately, among our patients, most of the irAEs were grade I/II (mild to moderate toxicity), which does not exclude serious and life-threatening ones (e.g., severe form of colitis, pneumonitis, encephalitis, toxic epidermal necrosis, myocarditis, ketoacidosis), which did not occur probably due to the small number of patients in our study. It is also possible for irAEs to occur in multiple organ systems at the same time, which occurred in 4 of our patients.

CONCLUSIONS

Based on the obtained results, we can conclude that immunotherapy certainly occupies an important place in the treatment of stage IV NSCLC. Namely, the rare occurrence of severe AE, which is a characteristic of cytotoxic chemotherapy, and the relative ease of treatment of irAEs that occur in immunotherapy, good overall survival and a later onset of disease progression open the door to the possibility of drastically improving the quality of life of these patients and extending their lifespan.

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