Unexpectedly long progression-free time in a patient with squamous cell carcinoma of the lung treated with Nivolumab – a case study

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**Abstract**

**Background:** In the reported case, our patient with lung cancer diagnosed as squamous cell carcinoma (SqCC) achieved eight times longer progression-free time (PFT; 25.3 months) than that obtained in the median of randomized clinical trials (3.5 months).

**Case Report:** A 61-year-old man presented for treatment due to a long-lasting cough and a type of pain in the chest, in good general condition. The patient had a smoking history when he was young. Computed tomography (CT) showed a lesion larger than 70 x 60 mm. The diagnosis was made on the basis of the bronchoscopic material. The prognosis was unfavorable and the tumor was inoperable. In the first line of treatment, chemotherapy with cisplatin was started. Due to the progression, second-line immunotherapy with Nivolumab was administered,
and was continued for a longer period of time. Treatment was well tolerated and there were no side effects reported. Therapy was however interrupted due to the patient's deteriorating condition and progression in the follow up CT examination. Finally the patient was qualified for palliative treatment with chemotherapy and zoledronic acid. Opioid medications were used to treat pain.

**Conclusion:** The patient lived for over 4 years, including over 2 years without progression. It therefore seems that there is a group of patients who respond exceptionally well to immunotherapy, but the identification of predictors requires further research.

**Keywords:** Lung Neoplasm; Immunotherapy; Progression-Free Survival

**Background**

Lung cancer is currently the most common malignant cause of death among men and the second most common among women worldwide, [1] as well as the second in terms of incidence and first in terms of mortality in Poland (both in men and women). [2] Squamous cell carcinoma accounts for approximately 30% of all non-small cell lung cancer (NSCLC) cases. [3]

Although therapy for early-stage SqCLC mimics other histological subtypes of NSCLC, limited therapeutic options are available for advanced SqCLC compared with lung adenocarcinoma. [4] Efforts to find an effective targeted therapy are complicated by the fact that mutations/alterations for which the targeted therapy has been approved are rare in SqCLC. [5] Therefore, until recently, the standard of care in the treatment of NSCLC has been platinum derivative-based chemotherapy applied in 4-6 cycles, which has been characterised by moderate efficacy, with high toxicity manifested by many side effects, [6] [7] while the preferred treatment among the patients with confirmed PD-L1 ≥50% has been pembrolizumab monotherapy [8], which may only be an option for less than 1/4 of the population – those potentially eligible for immunotherapy [9].

This paper presents the clinical case of a patient with SCC of the left lung who achieved an extremely long PFS of 25.3 months after under the Nivolumab immunotherapy.
Case Report

Patient information

A 61-years old patient was admitted to the Oncology Clinic in late 2018 due to a large (72 x 66 mm) tumor visualized during the CT examination at the Pulmonology Department. The patient reported dry cough and prickly pain in the sternum area, that had been manifesting since the May 2017. The patient had a smoking history when he was young. No other relevant medical, family, and psycho-social history was reported. No relevant past interventions.

Clinical findings

The patient was in good general condition. General examination showed no major abnormalities. Laboratory tests presented elevated C-Reactive Protein (CRP) concentration in the venous blood.

Timeline

The patient was admitted to the Pulmonology Department in the late 2017 and transferred to the Oncology Clinic immediately after obtaining the CT results, strongly suggesting the neoplastic nature of the lesion described. The patient was at risk of lung cancer due to age, size of the lesions and smoking history. The systematic treatment was conducted between 01/15 and 03/27/2018 06/15/2018 and 07/27/2020. Later he was qualified for the palliative treatment in the 08/2020.

Diagnostic Assessment

X-ray and CT scans were performed in the Pulmonology Department before the patient’s transfer to the Oncology Clinic.

In the X-ray examination suspected shadows (probable lesions) in the upper lobe of the left lung were visualised. The chest CT scan described a 72 x 66 mm tumor at the base of the segment 1/2, strengthening in the peripheral parts with an area of retrograde changes in the central part. The neoplastic lesion infiltrated the bronchial tube of this segment, which was only permeable in the closer part. The tumor also infiltrated thorax, descending aorta, and the left pulmonary artery. Significantly enlarged (26 x 12mm) lymph node by the aortic arch was also described.
Bronchoscopy with biopsy showed the presence of SqCLC (TNM stage T4N1), rendered on the biopsy material.

**Therapeutic Intervention**

Patient was qualified for treatment with neoadjuvant chemotherapy with cisplatin, vinorelbine. The systemic treatment was conducted between 01/15 and 03/27/2018. The patient was qualified for immunotherapy and was treated with nivolumab since 06/15/2018 until 07/27/2020. Treatment was well tolerated and there were no side effects reported. In follow-up CT scans a partial regression was notable. [Figure 1, 2]

**Follow-up and Outcomes**

*Figure 1* *Figure 2*

In follow-up CT examination dated on 06/04/2018, the progression was described, hence eliminating the possibility of surgical resection of the lesion. [Figure 3, 4] Therapy was however interrupted due to the patient's deteriorating condition and progression in the follow up CT examination described on 08/05/2020. [Figure 5, 6].

Finally the patient was qualified for palliative treatment with chemotherapy and zoledronic acid. Radiation therapy of the left sixth rib was also considered, but not introduced. Opioid medications were used to treat pain.
During the treatment at the Oncology Clinic the patient received 56 doses of nivolumab and reached the PFS of 25.3 months with the progression-free survival (PFS) amounted ca. 27.5 months.

**Figure 3**

**Figure 4**

**Figure 5**

**Figure 6**
Discussion

The case concerns a patient who, unfortunately, could not be qualified for radical surgical resection. This had two consequences, the first of which was the need to implement systemic therapy, and the second was the inability to accurately diagnose the histological type of the tumor based on the histopathological examination of the surgical material. Thus, in this case, the diagnosis is made on the basis of samples obtained during the biopsy and bronchoscopy.

The main limitation of this case study is the lack of surgical evidence regarding the diagnosis, although the material obtained from bronchoscopy may to some extent be sufficient or even considered conclusive equally. Another limitation may be the lack of data on the genetic basis of the case. The patient, however, lived in Poland from birth and did not belong to an ethnic minority, so it can be assumed that any observations may be the basis for possible hypotheses for further research, at least in relation to the European population.

In terms of assessing the effectiveness of immunotherapy, it seems to be essential to emphasize, that Nivolumab was used only in the second line of treatment after the prior neoadjuvant chemotherapy. However there seems to be a little indication that the first-line treatment was a factor that significantly prolonged the patient's life. This conclusion arises from the fact that during the chemotherapy there was a noticeable progression of the neoplasm. Thus, it can be considered that the progression-free time is due solely or mainly to immunotherapy.

The presumptive advantage of this study may be the relatively long follow-up time, probably resulting from the extremely favorable results of immunotherapy in terms of the expected prolongation of the patient's life.

The hope for improved treatment of inoperable patients with SqCLC is nivolumab, a fully human IgG4 immune checkpoint inhibitor 1 (PD-1) antibody [10]. Nivolumab has shown a much longer progression-free time compared with docetaxel in patients with advanced NSCLC after failure of first-line treatment [10, 11]. In November 2020, the European Commission registered the first dual immunotherapy consisting of nivolumab and ipilimumab added to 2 cycles of chemotherapy for patients with confirmed PD-L1 mutation. [12] This result was significantly superior to the median PFS, which was 3.5 months in randomised clinical trials [11].
As it can be seen from the presented description, the Nivolumab had two phases, during which the tumor underwent clinically significant changes. There was regression first, and only with the passage of time, progression. There are limited data on how, in the case of immunotherapy, the fact of partial regression affects the duration of PFS over the entire treatment period. The fact that partial regression took place, however, is not a sufficient explanation for such a long progression-free response. Therefore, it seems that the data on the presented case is not sufficient to clearly state what factors could be used to predict that the patient’s response would be so long.

However, the reported case clearly shows that in some patients response can be very long-drawn. The available literature suggests that there are numerous factors that make it possible to predict the response durability and quality. A side of the expression of immune checkpoint proteins (PD-1/PD-L1), being the key utility to determine the eligibility of patients, the sensitivity of tumors may depend on other factors, including other gene expression signatures and molecular tumor profiles [13,14] or Background Tumor mutational burden (TMB) [15]. They enable continuous research into new molecular and radiological biomarkers.

Therefore, it may be concluded, that there is a group of patients who respond better to nivolumab treatment, achieving a longer progression-free time, similar to the presented story of a patient with inoperable SCC. It seems that further studies should focus on the selection of patients who are more likely to have a long-term response to the immunotherapy used. Clinical practice indicates the presence of clinical features both in the patient himself and in the genetic profile of the tumour cell favourable for the application of immunotherapy. Nevertheless, it is necessary to await the results of clinical trials currently underway to demonstrate predictive factors of response to immunotherapy in order to obtain scientific proof of the subjective observations and opinions of oncologists using this therapy among their patients.

**Patient perspectives**

The patient's current prospects are unfavorable due to tumor progression, age within old age and continuation of palliative treatment, which did not result in patient death at least until the beginning of 2022. Further treatment should be primarily aimed at improving the patient's quality of life as much as possible.
Informed Consent

Regarding an anonymised case study, informed consent was not necessary under the local law. Treatment guidelines were followed during treatment. The case was not part of a clinical trial and had no features of a medical experiment. Nonetheless, the authors obtained the patient's consent to describe the stage of oncological treatment.

Conclusions

The patient lived for over 4 years, including over 2 years without progression. It therefore seems that there is a group of patients who respond exceptionally well to immunotherapy, but the identification of predictors requires further research.

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, Bray F. Cancer statistics for the year 2020: An overview. Int J Cancer. 2021; https://doi.org/10.1002/ijc.33588

2. Wojciechowska U, Didkowska J, Michalek I, Olasek P, Ciuba A. Nowotwory złośliwe w Polsce w 2018 roku. Polish National Cancer Registry; 2020; http://onkologia.org.pl/wp-content/uploads/Nowotwory_2018.pdf

3. Travis WD. Pathology of lung cancer. Clinics in chest medicine. 2002. 23.1:65-81.; https://doi.org/10.1016/S0272-5231(03)00061-3

4. Morgensztern D, Waqar S, Subramanian J, Gao F, Govindan R. Improving survival for stage IV non-small cell lung cancer: a surveillance, epidemiology, and end results survey from 1990 to 2005. J Thorac Oncol. 2009; https://doi.org/10.1097/JTO.0b013e3181ba3634

5. Socinski MA, Obasaju C, Gandara D, Hirsch FR, Bonomi P, Bunn PA Jr, Kim ES, Langer CJ, Natale RB, Novello S, Paz-Ares L, Pérol M, Reck M, Ramalingam SS, Reynolds CH, Spigel DR, Wakelee H, Thatcher N. Current and Emergent Therapy Options for Advanced Squamous Cell Lung Cancer. J Thorac Oncol. 2018; https://doi.org/10.1016/j.jtho.2017.11.111

6. Gandara DR, Hammerman PS, Sos ML, Lara PN Jr, Hirsch FR. Squamous cell lung cancer: from tumor genomics to cancer therapeutics. Clin Cancer Res. 2015; https://doi.org/10.1158/1078-0432.CCR-14-3039
7. Oun R, Moussa YE, Wheate NJ. The side effects of platinum-based chemotherapy drugs: a review for chemists. Dalton transactions. 2018.; https://doi.org/10.1039/C8DT00838H

8. Krzakowski M, Jassem J, Antczak A, et al. Cancer of the lung, pleura and mediastinum. Oncol Clin Pract 2019; http://onkologia.zalecenia.med.pl/pdf/zalecenia_PTOK_tom1_03_Nowotwory_pluca_i_oplucnej_20190517.pdf

9. Dietel M, Savelov N, Salanova R, Micke P, Bigras G, Hida T, Antunez J, Guldhammer Skov B, Hutarew G, Sua LF, Akita H, Chan OSH, Piperdi B, Burke T, Khambata-Ford S, Deitz AC. Real-world prevalence of programmed death ligand 1 expression in locally advanced or metastatic non-small-cell lung cancer: The global, multicenter EXPRESS study. Lung Cancer. 2019; https://doi.org/10.1016/j.lungcan.2019.06.012

10. Paz-Ares, Luis, et al. Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC). (2015): LBA109-LBA109.; https://ascopubs.org/doi/abs/10.1200/jco.2015.33.18_suppl.lba109

11. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Arén Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015; https://www.nejm.org/doi/full/10.1056/nejmoa1504627

12. E. Słomska, P. Niemczyk-Szechowska, P. Ryś, M. Niewada, W. Wrona. Rak pluca 2021 - Raport; 2021; https://immuno-onkologia.pl/wp-content/uploads/2021/06/rak-pluca-2021-Raport.pdf

13. Memmott RM, Wolfe AR, Carbone DP, Williams TM. Predictors of Response, Progression-Free Survival, and Overall Survival in Patients With Lung Cancer Treated With Immune Checkpoint Inhibitors. J Thorac Oncol. 2021; https://doi.org/10.1016/j.jtho.2021.03.017

14. Blons H, Garinet S, Laurent-Puig P, Oudart JB. Molecular markers and prediction of response to immunotherapy in non-small cell lung cancer, an update. J Thorac Dis. 2019; https://jtd.amegroups.com/article/view/26414/19776

15. He B, Dong D, She Y, et al. Predicting response to immunotherapy in advanced non-small-cell lung cancer using tumor mutational burden radiomic biomarker. Journal for ImmunoTherapy of Cancer. 2020; https://jitc.bmj.com/content/8/2/e000550