International Journal of Case Reports (ISSN:2572-8776)

Immunotargeted Monotherapy by Anti-PD-1 in Patients with Primary Non-small Cell Lung Cancer

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ABSTRACT

The 5-year survival rate of advanced non-small cell lung cancer is less than 5%. In recent years, immunotherapy represented by PD-1 antibody has become the standard treatment recommended by many lung cancer guidelines. With the treatment, the total survival time and quality of life have been significantly prolonged in patients with advanced Primary non-small cell lung cancer (NSCLC). In this study, the domestic anti-PD-1 monoclonal antibody, Camrelizumab, combined with chemotherapy was used to treat advanced non-small cell lung cancer. The efficacy of Camrelizumab and occurrence of cutaneous capillary hyperplasia (CCEP) were analyzed.

Keywords: Primary non-small cell lung cancer; Camrelizumab; Cutaneous capillary endothelial proliferation (CCEP)

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How to cite this article:

SUN Liqiu, ZHANG ge, YU Tingting, TANG Songyan, WANG Hongli. Immunotargeted Monotherapy by Anti-PD-1 in Patients with Primary Non-small Cell Lung Cancer. International Journal of Case Reports, 2020; 4:120

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Introduction

Lung cancer is one of the malignancies with the highest morbidity and mortality in the world ¹. Every year, 1.6 million people are diagnosed with lung cancer, accounting for 13% of newly diagnosed cancers. 1.4 million patients died of lung cancer, accounting for 18% of cancer-related deaths ². The mortality and incidence of lung cancer in China are among the highest in the world ³. Among the numerous subtypes of lung cancer, non-small cell lung cancer (NSCLC) accounts for 80%-85%, but surgical resection is not recommended for more than 70% ⁴. Despite advances in the treatment of non-small cell lung cancer, the prognosis remains poor, with a five-year survival of only 15%. ⁵ Less than a third of the NSCLC patients who were early detected received surgical resection. Furthermore, 5-year survival rate of unresectable III stage b and IV NSCLC patients was only 5% and 2% respectively ⁶. NSCLC includes multiple types like adenocarcinoma, squamous cell carcinoma, large cell carcinoma and bronchiolar and alveolar carcinoma. Currently, chemotherapy and targeted therapy are used in clinical treatment. In recent years, immunotherapy by PD-1 antibody has become the standard treatment recommended by many lung cancer guidelines. Immunotherapy has changed the survival period of lung cancer. The five-year survival rate has increased from 5-16%, which is a leap that has not been made since ancient times. ⁷ Although high expression of PD-L1 is the key for lung cancer patients to decide whether to use immunotherapy, the correctness of choosing immunotherapy for patients with low expression cannot be denied. Data shows that the effective rate in lung cancer patients with low expression of PD-L1 is also 10-16%. ⁸ Here we reported two cases of NSCLC patients with anti-PD-L1 treatment and discussed its possible adverse reactions.

Case one: Anti-PD-L1 treatment for non-small cell lung cancer case

Basic information of cases

This case is an elderly patient with primary non-small cell lung cancer who received immunotherapy with massive hemoptysis and low expression of PD-L1.

Name: Li xx, gender: male, age: 79 years old, weight :70kg, height :170cm, body surface area :1.80m², general status score: 2 points, pain score: 0 points. Normal health, denied the history of diabetes, hypertension, cardiovascular history, history of toxic hepatitis, typhoid fever, tuberculosis and its close contact history. No history of drug allergy, food allergy, major trauma, surgery, blood transfusion. History of vaccination is unknown. Brief history: in early June 2019, without obvious inducement, the patient developed cough with white sputum, ribs pain but no fever. Then he went to Dongning people's hospital and checked with chest CT. CT result showed space-occupying lesions in the right lung with obstructive inflammation. On July 4, 2019, an electronic bronchoscopy was performed in Mudanjiang Hongqi hospital. The pathological findings include: (the dorsal segment of the lower lobe of right lung) biopsy, squamous cell carcinoma (non-keratinized type). Immunohistochemical markers showed: P40 (+), ck5/6 (+), NapsinA(-), TTF1(-). Lung enhanced CT examination was performed in Mudanjiang hongqi hospital on July 10, 2019, and the results were as follows: 1. Occupied right lower lobe; possibility of central lung CA, recommendation of biopsy; 2. Thickening of the food tube wall, recommendation of further examination by upper gastrointestinal angiography; 3. Right pleural thickening and calcification; 4. Degenerative changes in thoracic vertebra. The patient chose to take Chinese medicine for more than a month rather than systematic treatment, but received no

beneficial. In early September 2019, he was admitted to hospital due to cough, sputum cough and multiple hemoptysis (large volume, bright red color, about 100ml per day). Clinical diagnosis: lung squamous cell carcinoma stage IIIC; Gene test: no mutation site was detected; Low-expression of PD-L1 (< 49%); Tumor mutation load (TMB): 12.516mutation/Mb; Microsatellite instability (MSI): MSI stable type (MSS). Treatment: the hemoptysis volume was about 150 ml on 2019-09-05 on the day of admission. The hemostatic treatment was immediately given (pituitrin 12U once a day + bazuting 2ml twice a day). On 2019-09-14, the hemoptysis volume was about 50 ml, with bright red color. On 2019-09-20, the Hemoptysis volume was about 20ml, with bright red color. On 2019-09-27, patient started to receive immunotherapy for three cycles: (200mg carilizumab)*3cs. On 2019-09-29, The amount of hemoptysis was about 5ml. No hemoptysis has occurred since 2019-10-07.

Case treatment

Before treatment

CT findings: no obvious abnormal density foci in brain parenchyma, no obvious expansion of ventricular system, obvious widening and deepening of sulcus, fissure and cistern, middle line structure, no obvious abnormality in skull structure. Lumpy soft tissue shadow was seen in the right hilar area, the cross section of the lesion was about 7.8*10.1cm. The boundary was unclear. The distal end showed patchy and nodular slightly dense shadow. The boundary was fuzzy.

Nodules were seen in the mediastinal 4R, 5, 6, 7 areas. Bilateral pleural localized thickening. Some showed calcified density change. No effusion was seen in the pericardium and thorax. The liver volume was not large, and there were round low-density foci in the liver, with clear boundaries and uniform density. The bile duct and portal vein inside and outside the liver were not wide. The gallbladder was not large. The wall was not thick, and there was no obvious abnormal density in the capsule. No obvious abnormality was found in pancreas, spleen and kidney. The bladder was well filled, with patchy dense shadow on the left posterior wall of the bladder, enlarged prostate. No obviously enlarged lymph nodes in the pelvic cavity. No pelvic effusion, no obvious abnormalities, and poor shape of the right ischium.

Diagnoses:

- (1) Space-occupying lesions in the right lung; Possible lung cancer with obstructed lesions; Recommend to confirm with Microscopic examination
- (2) Mediastinal lymph node enlargement
- (3) Intrahepatic cystic lesions; Recommend further examination
- (4) Bladder changes; Recommend further examination
- (5) Prostatic hyperplasia
- (6) The right ischium is changed, Recommend further examination
- (7) Brain atrophy

	Name	Result	Warming	Reference range
1	SCC	1.0		<=1.5 ng/ml
2	CEA	2.59		<=3.40 ng/ml
3	CA125	33.45		0-35 U/ml
4	CYFRA-21-1	40.79	↑	<3.30 ng/ml
5	NSE	17.03	↑	<16.3 ng/ml

Both sides of the clavicle had multiple hypoechoic nodules with clear boundaries. The size was about 1.0*0.6cm above the right clavicle while 1.2*0.5cm above the left clavicle.

Diagnoses: multiple bilateral supraclavicular lymph nodes.

After three cycles of immunotherapy

CT findings: multiple spots and patchy low-density shadows in the right basal ganglia area and the center of bilateral semiovale, clear boundaries, no obvious expansion of the ventricular system, obvious widening and deepening of the sulcus, fissure and cisterna, middle line structure, and no obvious abnormalities in skull structure. Right hilar region had massive soft tissue shadow (7.1 * 7.2 cm) with gas inside the cavity and none clear boundaries. The distal end is patchy and nodular with a slightly higher density shadow, and the boundary was blurred. Nodule-like shadow (0.5 cm in diameter) can be seen in the left lower lobe near the interpleural pleura. The boundary is clear. Nodular shadows were in mediastinal 4 r, 5, 6, 7 area. Localized thickening was in bilateral pleura, Partial calcification-like density change, pericardium and chest did not see the effusion. The liver was not large. Round-shaped low-density lesions were in the liver, the larger is about 1.0 cm in diameter. The Boundaries were clear and uniform in density. The bile ducts inside and outside the liver and portal vein were not wide, the gallbladder was not large, the

wall was not thick, and there was no obvious abnormal density in the capsule. No obvious abnormality was found in pancreas, spleen and kidney. The bladder was well filled, with patchy dense shadow on the left posterior wall of the bladder, enlarged prostate, no obviously enlarged lymph nodes in the pelvic cavity, no pelvic effusion, multiple nodules in the bilateral inguinal region, and poor ischial morphology on the right.

Diagnoses:

- (1) The lesions of right lung space occupation were reduced compared with the pre-treatment
- (2) Mediastinal lymph node
- (3) Intrahepatic cystic lesions, the same as pre-treatment
- (4) Bladder changes, the same as pre-treatment
- (5) Prostatic hyperplasia
- (6) Changes in the right ischium, the same as pre-treatment
- (7) Bilateral cranial encephalopathy: it is considered that part is a cavity stalk and part is an ischemic change. If necessary, check by MRI.
- (8) Brain atrophy

	Name	Result	Warming	Reference range
1	SCC	1.2		≤ 1.5 ng/ml
2	CEA	0.73		≤ 3.40 ng/ml
3	CA125	18.89		0-35 U/ml
4	CYFRA-21-1	6.21	↑	< 3.30 ng/ml
5	NSE	11.25		< 16.3 ng/ml

Both sides of the clavicle had multiple hypoechoic nodules with clear boundaries. The size was about 0.9×0.6 cm above the right clavicle while 0.9×0.5 cm above the left clavicle

Comparison of efficacy: evaluation of efficacy: PR

September 10, 2019 November 28, 2019

Case summary

Immunotherapy is effective. We also found adverse reactions including reactive capillary hyperplasia (RCCEP). After one month of immunotherapy, Tumor-like RCCEP appeared mainly in the face and scalp.

Case two: Adverse reactions of anti-PD-L1 in the treatment of non-small cell lung cancer

The marketing time of anti-PD-1 monoclonal antibody was relatively short, but it shows

completely different immune related adverse events (irAEs) from traditional cytotoxic drugs and molecular targeted drugs, which has attracted great attention of domestic and foreign scholars. The most common irAEs mainly involve skin, colon, endocrine organs, liver and lungs, and also include some rare reactions reported in the literature, such as neuropathy and myocarditis. In this case, we mainly discussed the treatment and treatment of the Careilizumab

specific adverse reaction, namely drug - related cutaneous capillary proliferation (CCEP).

According to morphological manifestations, CCEP is roughly divided into five types: "red nevus", "pearl", "mulberry", "patch" and "tumor", of which "red nevus" and "pearl" are the most common. Multiple types of cutaneous capillary hyperplasia could be found on the body surface of the same patient. Sometimes we can see switches between different types, such as "red nevus" that can be enlarged into "pearl type", "pearl type" that can be enlarged into "tumor type" (Figure 1). The earliest sites of CCEP are face, scalp, neck and upper chest wall, and then gradually appear on the skin of the abdominal

wall, back, limbs, buttocks and external genitalia. They are usually bright red dots with a diameter of less than 2 mm (red mole type), with a small number of patches or mulberries. The red moles gradually develop into "pearl-like" skin nodules, which are bright red or dark red, and easy to break. They can partially develop into a "tumor-like type" (≥ 10 mm in diameter). The fastest time of occurrence is 10 days after medication, but most appear during 2 to 4 weeks. With the increase of treatment time, their sizes gradually increase. The compound dexamethasone acetate cream (Pi Yan Ping) was applied externally, but it was not effective. It is difficult to cure the insensitivity to glucocorticoid treatment by surgery or physical therapy such as laser and freezing.

A "red nevus"; B. "pearl"; C. "mulberry type"; D. "plaque type" E. "tumor type"

Figure 1: general classification of CCEP ⁹

Basic information and treatment of the case

Name: Li xx, gender: female, age: 56 years old, weight: 65kg, height: 167cm, body surface area :1.72m², general status score :1 point, pain score: 0 point. Normal health, denied history of diabetes, hypertension, cardiovascular history, history of viral hepatitis, typhoid fever, tuberculosis and close contact, no history of drug allergy, food allergy, major trauma, surgery, blood transfusion and vaccination history unknown.

Brief medical history: in early April 2019, the patient presented pain in the left quarter costal region without any cause, occasional dry cough and no fever. Chest CT examination showed strippebral shadows in the upper lobe of the left lung and pleural effusion in the left lung. Anti -

inflammatory week reexamination increased pleural effusion. Exfoliating cells of pleural effusion showed malignant tumor cells, tending to adenocarcinoma. ECT: multiple abnormal bone metabolism in the whole body. Genetic test: no mutation sites were detected.

Diagnoses: lung adenocarcinoma stage IV malignant pleural effusion bone metastasis.

Treatment: 1 cycle of systemic chemotherapy was started on May 10, 2019. The scheme was: pemetrexed 0.8g static point + 60mg lobaplatin (divided pleural injection). Chemotherapy combined with immunotherapy was started on June 04, 2019 for 3 cycles. The regimen was: pemetrexed 0.8g static point + loplalin 60mg (divided chest infusion) + calirizumab 200mg static

point.

Bone therapy: 4mg ibandronate sodium once every 21 days

The patient presented multiple bright red skin lesions on the face, scalp, neck and upper chest

wall after 15 days of treatment, initially like "red mole". As the course of treatment increased, the skin nodules gradually rose and increased, and some of the larger tumor-like changes were observed on the face and scalp (figure 2019-09-06).

(FIG. 2019-9-06)

Apatinib 250mg was taken orally once a day on September 6, 2019, and the patient complained of dizziness and headache for 2 days. Monitoring of blood pressure indicated hypertension, with a maximum blood pressure of 210/100mm hg, which was considered to be related to Apatinib. Apatinib 250mg was adjusted for oral

administration every two days. The monitoring of blood pressure and other vital signs showed no obvious abnormalities, and the patients had no complaints of discomfort. During the period of combination with Apatinib, there were no new lesions were found. The original lesions gradually shrank, darkened and partially disappeared.

Photo: 24 September 2019

On October 15, 2019, the patient was treated with calrizumab for 5 cycles, as shown in the figure

Treatment evaluation PR in July 2019, drainage tube was removed. Single-drug chemotherapy

combined with immunotherapy for 2 cycles began on August 13, 2019. The regimen was:

pemetrexed 0.8g static point + calirizumab two days.

200mg static point, apatinib 250mg oral every

Treatment chart Before treatment, 2 cycles of treatment, 4 cycles of treatment, 2 cycles of maintenance treatment

Summary of case two

Conclusion: after 15 days of administration of 200mg of Crillizumab, CCEP was induced. Administration of Apatinib 250mg every two days for 1 week was effective for CCEP and the treatment showed no obvious adverse reactions. The combination therapy was tolerable, and the compliance of simple patients was good.

Carillizumab combined with chemotherapy and Apatinib was effective and well tolerated in the treatment of advanced non-small cell lung cancer.

Conclusion

There are a lot of cancer treatment issues that need to be addressed, such as the starting point of antibody use, duration of antibody use, co-use strategies with other treatment options, identification and evaluation of priority treatment targets, and measures to overcome antibody resistance.¹⁰ In the field of combination therapy, treatments based on monomolecular and monocytogenic mechanisms, such as PD-1 antibody combination therapy model, suggest that such a multi-pathway combination therapy strategy could produce synergistic enhancement effect in tumor immunotherapy.¹¹ The preclinical model

of CTLA-4 and PD-1 combined blockade showed a promising result and no toxic reaction was generated by the regimen¹². The clinical efficacy of checkpoint blocking antibodies in monoclonal antibody therapy has been confirmed. The next step is to evaluate the safety and efficacy of combination therapy. The most notable aspect of the relevant studies is that the mechanism of PD-1 targeted therapy is different from traditional chemotherapy and existing molecular targeted therapy. Therefore, a new evaluation mechanism for its efficacy needs to be introduced.

To sum up, PD-1 is one of the important checkpoints for tumor development. The PD-1 pathway is a promising target for the treatment of NSCLC.

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