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Exploration on Short Term Efficacy and Safety of PD-1 Immunotherapy Combined with Neoadjuvant Chemotherapy in the Treatment of Non-small Cell Lung Cancer

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Abstract: The purpose of this study is to explore the short-term efficacy and safety of PD-1/PD-L1 immunotherapy combined with neoadjuvant chemotherapy in the treatment of resectable non-small cell lung cancer. Collect clinical data of 89 non-small cell lung cancer patients who underwent PD-1/PD-L1 immunotherapy combined with neoadjuvant chemotherapy from January 2020 to December 2022 in the first and second extrathoracic wards of our hospital, aged 50.0 to 82.0 (68.0 ±8.5) years old. Retrospective analysis of the imaging data and pathological changes of patients before and after PD-1/PD-L1 immunotherapy combined with neoadjuvant chemotherapy treatment, recording the adverse reactions that occurred during the treatment process, with objective response rate, main pathological response rate, and pathological complete response rate as the main observation indicators. The results showed that after PD-1 immunotherapy combined with neoadjuvant therapy, all patients successfully underwent thoracoscopic radical resection of lung cancer. According to the RECIST 1.1 standard evaluation analysis, 16 patients achieved complete remission and 36 patients achieved partial remission, with an objective remission rate of 58.43%; There were 17 PCR patients and 61 MPR patients, with a main pathological response rate of 87.64%. The main adverse reactions of the patients were Hypoalbuminemia, decreased appetite and nausea. Most patients were mild, and no drug intervention was needed; There were no deaths or tumor metastasis within one month after surgery. Therefore, the combination of PD-1/PD-L1 immunotherapy and neoadjuvant chemotherapy for resectable non-small cell lung cancer is safe and can effectively improve postoperative symptoms and promote patient recovery.

1. Introduction

At present, the incidence rate and mortality of lung cancer in the world are increasing year by year, and it is one of the most common and Case fatality rate malignant tumors in the world [1]. According to the relevant data released by the International Agency for Research on Cancer in 2020,

lung cancer ranks second in the incidence rate of malignant tumors, but the number of deaths caused by lung cancer each year ranks first [2]. According to the pathological classification of cancer cells, primary lung cancer can be classified as non-small cell lung cancer (Non small cell lung cancer, NSCLC) and small cell lung cancer (SCLC), among which NSCLC is the most common type of lung cancer, accounting for approximately 85% of the total primary lung cancer [2]. The main pathological types of NSCLC include adenocarcinoma, squamous cell carcinoma, large cell lung cancer, and other rare types of lung cancer [3]. In NSCLC patients diagnosed for the first time, less than 25% of patients were diagnosed with early tumors, and about 2/3 of patients could receive radical Sex therapy [4, 5]. Most patients were in the middle and late stages of tumor at the time of initial diagnosis. Surgery is the best way to resectable NSCLC, but there is still a risk of recurrence or metastasis after surgery. According to research [6], the overall survival (OS) of NSCLC patients at 5 years after surgery will decrease with the increase of clinical staging of their malignant tumors, and the 5-year OS rate of patients in the advanced stage of the tumor is even lower than 10% [7]. In order to improve the prognosis of patients, postoperative adjuvant therapy was administered to patients who meet the indications. It was found that platinum containing dual drug adjuvant therapy can improve the recurrence risk of patients, leading to an increase in their 5-year OS rate [8]. However, the clinical efficacy of adjuvant therapy is not significant. Therefore, in order to further improve the prognosis, relevant trials of neoadjuvant chemotherapy were conducted. Through analysis, it was found that the 5-year OS rate of patients can be increased by about 5% [8]. However, after years of clinical efficacy observation, the researchers are not very satisfied with the clinical efficacy of neoadjuvant chemotherapy [9], especially for patients with lymph node metastasis. Therefore, American scholar William Coley first attempted the use of immunotherapy for the treatment of malignant tumors, and in 1992, Aldeslekin became the first immunotherapy drug approved by the US FAD. Subsequently, several immunotherapy drugs emerged one after another. In recent years, immune checkpoint inhibitors have gradually been applied in clinical practice, enriching the treatment methods for NSCLC in clinical practice. The main immune checkpoints currently include programmed cell death receptor 1 (PD-1) and programmed cell death ligand 1 (PD-L1). Research has shown that PD-L1 is mainly expressed on the surface of tumor cells and plays an important role in the response of T cells and B cells. The interaction between PD-L1 and PD-1 may produce negative regulatory factors, and the expression of PD-L1 on tumor cells may directly affect T cell lysis, as it binds to the PD-1 receptor on T cells to form a binding body that effectively prevents dissolution. However, after binding, T cells lose their ability to inhibit tumor growth, ultimately leading to T cell response being inhibited [10-13]. Therefore, this study retrospectively analyzed 89 patients treated with PD-1/PD-L1 immunotherapy combined with neoadjuvant chemotherapy to explore its efficacy and safety.

2. Research methods and objects

2.1. Clinical data

Retrospective analysis of the clinical data of 89 non-small cell lung cancer patients who underwent PD-1/PD-L1 immunotherapy combined with neoadjuvant chemotherapy from January 2020 to December 2022 in the first and second extrathoracic wards of our hospital. Inclusion criteria: (1) Confirmed as NSCLC through pathological examination, with clinical diagnosis staging ranging from stage IA to stage IIIB; (2) No distant metastasis of lung cancer has occurred yet; (3) Patients receiving PD-1/PD-L1 immune combined with neoadjuvant chemotherapy treatment plan; (4) The Eastern Cooperative Oncology Group (ECOG) in the United States has a score of 0-1; (5) At least 1 measurable lesion in imaging; (5) Eliminate severe liver, kidney, heart, and lung dysfunction; (6) Sign an informed consent form. Exclusion criteria: (1) Individuals who are

physically weak and unable to tolerate surgery or patients with severe systemic diseases or severe organ dysfunction; (2) There are contraindications to using immune checkpoint inhibitors; (3) The presence of sensitive gene mutations is not suitable for immunotherapy.

2.2. Research Methods

2.2.1. Therapeutic method

The patient received neoadjuvant therapy using a combination of PD-1/PD-L1 immune checkpoint inhibitors and platinum containing dual drug chemotherapy regimen, among which PD-1/PD-L1 immune checkpoint inhibitors are currently approved drugs on the market. The chemotherapy regimen refers to the advanced NSCLC treatment regimen in the diagnosis and treatment guidelines for non-small cell lung cancer. After 2-4 cycles of neoadjuvant immunotherapy combined with chemotherapy, the patient underwent preoperative evaluation, including blood routine, biochemical indicators, coagulation function, tumor marker examination, chest imaging examination, etc. After evaluation, lesion site resection and lymph node dissection were performed.

2.2.2. Evaluation method

Based on the imaging data before and after chemotherapy, evaluate the efficacy of chemotherapy according to the Solid Tumor Efficacy Evaluation Standard 1.1 (RECIST 1.1), and record the objective response rate [2,8]. According to the effectiveness of treatment, it can be divided into: progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR). The postoperative pathological efficacy evaluation can be divided into: (1) PCR: refers to the complete absence of active tumor cell residues observed on the postoperative pathological specimen slices; (2) MPR: Refers to the observation of active tumor cell residues ≤ 10% on postoperative pathological specimen sections; (3) Pathological examination of the excised lung tissue and lymphatic tissue was performed after surgery without reaching pathological grade. After each chemotherapy, the general condition of the patient is recorded and blood samples are checked. We refer to U.S. Common Adverse Reaction Terminology Assessment Standard Version 5.0 to record adverse reactions and record the patient's mortality within one month after surgery to assess the safety of treatment [8].

2.2.3. Statistical methods

SPSS 27.0 software was used to conduct statistical analysis on the data collected in this study, and rank sum test was used to analyze the non-Normal distribution measurement data. For Normal distribution data, the measurement data shall be analyzed by t-test; The counting data is described using frequency and percentage (%). When calculated, $P<0.05$ indicates a statistically significant difference.

3. Results

3.1. General Information Results

A total of 89 patients were collected, including 72 males and 17 females, aged 50.0 to 82.0 (68.0 ± 8.5) years old. Among them, 67 were squamous cell carcinoma and 22 were adenocarcinoma. The ECOG scores are all 0-1 points. Have a history of smoking. 35 cases of PD-L1 expression were positive (≥ 1%), of which 12 cases were ≥ 50%. Before chemotherapy, imaging showed that the maximum diameter of the tumor was 30.01-79.24mm, with an average of (48.12 ± 8.36) mm. After

chemotherapy, the maximum diameter of the tumor was 16.92-51.33mm, with an average of (32.74 ± 10.73) mm. The clinical staging was divided into 8 cases of stage I A, 9 cases of stage I B, 13 cases of stage II B, 31 cases of stage III A, and 28 cases of stage III B. See Table 1.

Table 1: General Patient Information Results (%)

item	category	Number of cases	Percentage (%)
age	<60 years	37	41.57%
	≥60years	52	58.43%
gender	Male	72	80.90%
	Female	17	19.10%
Do you have a history of smoking	yes	71	79.78%
	no	18	20.22%
Pathological credit type	Squamous cell carcinoma	67	75.28%
	adenocarcinoma	22	24.72%
ECOG rating	0	43	48.31%
	1	46	51.69%
PD-L1 expression	≥50%	22	24.72%
	≥1%and<50%	35	39.33%
	<1%	32	35.96%
clinical stages	stage IA	8	8.99%
	stage IB	9	10.11%
	stage IIB	13	14.61%
	stage IIIA	31	34.83%
	stage IIIB	28	31.46%

3.2. Surgical results

Table 2: Surgical Results of 89 Patients (%)

item	category	Number of cases	Percentage (%)
extent of disease	Right whole lung	1	1.12%
	right upper lobe	19	21.35%
	Middle upper lobe of right lung	2	2.25%
	Middle and lower lobe of right lung	2	2.25%
	inferior lobe of right lung	17	19.10%
	Left whole lung	2	2.25%
	left upper lobe	21	23.60%
	Middle upper lobe of left lung	3	3.37%
	Middle and lower lobe of left lung	2	2.25%
	Left lower lobe of lung	20	22.47%
operative time	<60min	89	100.00%
	≥60min	0	0.00%
Intraoperative bleeding volume	<50ml	89	100.00%
	≥50ml	0	0.00%
Postoperative patient hospitalization time	<10d	89	100.00%
	≥10d	0	0.00%
Time for placing thoracic drainage tube	<7d	89	100.00%
	≥7d	0	0.00%
Have any complications occurred	yes	4	4.49%
	no	85	95.51%

After completing preoperative evaluation, all patients successfully underwent lung cancer radical

surgery, including 30 cases of right whole lung, 7 cases of right upper lobe, 10 cases of right lower lobe, 18 cases of left whole lung, 11 cases of left upper lobe, and 31 cases of left lower lobe. The surgical time was 73.10 to 276.23 (122.71 ± 47.75) minutes. The intraoperative bleeding volume was less than 50 mL and no blood transfusion was performed. The postoperative hospitalization time of all patients was less than 10 days. The postoperative placement time of the thoracic drainage tube is less than 5.5 days. Three cases developed postoperative pulmonary infections and improved after treatment. One case developed persistent pulmonary leakage and was cured after closed thoracic drainage treatment. See Table 2.

3.3. Evaluation of patient treatment effectiveness

The research results showed that after neoadjuvant immunotherapy combined with chemotherapy, 11 patients were in PD, 23 patients were in SD, 36 patients were in PR, and 16 patients were in CR. No residual cancer tissue was found, achieving complete pathological remission. See Table 3.

Table 3: Evaluation of tumor efficacy after treatment in patients (%)

Stages	Number of cases	Percentage (%)
progressive disease	11	12.36%
stable disease	23	25.84%
partial response	36	40.45%
complete response	16	17.98%

3.4. Postoperative pathological efficacy evaluation of patients

The research results showed that after neoadjuvant immunotherapy combined with chemotherapy, 17 patients achieved PCR, accounting for 19.10%, 61 patients achieved MPR, accounting for 68.54%, and 11 patients did not achieve pathological remission, accounting for 13.36%. See Table 4.

Table 4: Postoperative Pathological Efficacy Evaluation of Patients (%)

Stages	Number of cases	Percentage (%)
PCR	17	19.10%
MPR	61	68.54%
Failure to achieve pathological remission	11	13.36%

3.5. Adverse reactions of PD-1/PD-L1 immunotherapy combined with neoadjuvant chemotherapy

All 89 patients received neoadjuvant therapy with PD-1/PD-L1 immunotherapy combined with chemotherapy. Among them, 26 patients received 2 cycles of neoadjuvant therapy, 33 patients received 3 cycles of treatment, and 30 patients received 4 cycles of treatment. All 89 patients experienced varying degrees of treatment-related adverse reactions, with nausea being the main adverse reaction. Most patients were classified as Grade 1 and did not require medication intervention, while a few Grade 2 patients followed medical advice to use medication for intervention. In all adverse reactions, the clinical manifestations were mainly decreased appetite, nausea and general fatigue, and laboratory examinations were mainly Hypoalbuminemia and increased Alanine transaminase. The adverse reactions of patients were mainly grade 1. There were 25 cases of grade 3-5 adverse reactions, of which 2 cases were grade 3 anorexia, 5 cases were grade 3 nausea, 6 cases were grade 3 and 3 cases were grade 4 patients with decreased neutrophil count, 3

cases were grade 3 rash, and 6 cases were grade 3 Leukopenia. See Table 5.

Table 5: Treatment related adverse reactions in 89 patients (%)

Adverse reactions	Level 1	Level 2	Level 3	Level 4	Level 5
Hypoproteinemia	13(14.61%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Loss of appetite	46(51.69%)	0(0.00%)	2(2.25%)	0(0.00%)	0(0.00%)
Nausea	24(26.97%)	27(30.33%)	5(5.62%)	0(0.00%)	0(0.00%)
Generalized fatigue	36(40.45%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Alanine transaminase increased	8(8.99%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Cough	6(6.74%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Reduced neutrophil count	0(0.00%)	0(0.00%)	6(6.74%)	3(3.37%)	0(0.00%)
Hypokalemia	4(4.49%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Muscle soreness	4(4.49%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Anemia	6(6.74%)	2(2.25%)	0(0.00%)	0(0.00%)	0(0.00%)
Increased Alkaline phosphatase	3(3.37%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Diarrhea	7(7.87%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Rash	0(0.00%)	0(0.00%)	3(3.37%)	0(0.00%)	0(0.00%)
Reduced platelet count	0(0.00%)	4(4.49%)	0(0.00%)	0(0.00%)	0(0.00%)
Leukopenia	1(1.12%)	2(2.25%)	6(6.74%)	0(0.00%)	0(0.00%)

4. Discussions

NSCLC has a variety of clinical treatment methods, including surgery, chemotherapy, radiotherapy, Targeted therapy, immunotherapy, and so on. The formulation and selection of treatment plans are closely related to tumor stage. Research has confirmed [14] that for NSCLC in stage IIIA or IIIB, if there is no N2 lymph node metastasis positive, surgical resection is the preferred treatment method. For patients with N2 lymph node metastasis positive, chemotherapy or radiotherapy can be administered first, followed by surgical resection [14]. Chemotherapy drugs play a crucial role in anti-tumor treatment and have become the main treatment method for advanced lung cancer patients. The reduction and elimination of tumor cells during chemotherapy in patients provides the possibility for successful surgical removal of tumor cells, and neoadjuvant chemotherapy has been proven to effectively improve the prognosis of surgical patients. In recent years, tumor Targeted therapy and immunotherapy have also been tried to be applied to new adjuvant therapy. Immunotherapy includes immunocheckpoint inhibitors, CART cell therapy, Cancer vaccine, etc. Among them, immunocheckpoint inhibitors are the most important treatment methods. The main therapeutic mechanism is that the drug acts on programmed cell death protein-1 (PD-1), blocking the binding of PD-1 to its receptors PD-L1 and PD-L2, with the aim of inhibiting tumor growth. At present, immunocheckpoint inhibitors for the treatment of advanced lung cancer include Pembrolizumab, atezumab, Bevacizumab, and navumab. The combination of neoadjuvant chemotherapy has a significant effect on NSCLC [8].

The results of this study showed that the objective response rate of PD-1/PD-L1 immunotherapy combined with neoadjuvant chemotherapy for NSCLC patients was 58.43%, which is basically consistent with the research results of Liu Yutao et al. [15], which reported 5 patients with stage II to III NSCLC who received neoadjuvant immunotherapy combined with chemotherapy, with an objective response rate of 66.7%. In addition, in the study of Pembrolizumab combined with neoadjuvant chemotherapy for 11 patients with non-small cell lung cancer reported by Li Yixing et al. [8], 3 patients achieved complete remission and 5 patients achieved partial remission, with an

objective remission rate of 72.7%, which is highly similar to the results of this study. Moreover, the results of this study also showed that 17 patients achieved PCR, accounting for 19.10%, 61 patients achieved MPR, accounting for 68.54%. The main pathological response rate was 87.64%, and the proportion of patients who did not achieve pathological response was less than 15%. This is consistent with the research results of domestic scholars Bai Yue [16], Zhao et al. [17] used immune checkpoint inhibitor neoadjuvant therapy in 349 patients with NSCLC and conducted a meta-analysis. Among them, 159 patients (45.6%) showed primary pathological remission, 76 patients (21.8%) achieved pathological complete remission, and 144 patients received preoperative neoadjuvant therapy with immune checkpoint inhibitor combined with chemotherapy. The primary pathological remission rate was 66.7%, and the pathological complete remission rate was 35.4%. The analysis results indicate that chemotherapy combined with immune checkpoint inhibitors may have better effects than using immune checkpoint inhibitors alone. According to the NCCN guidelines [14], the expression of PD-L1 is not positively correlated with the efficacy of immunotherapy. Patients with positive PD-L1 expression may have a better response to immunotherapy, but there is still a possibility of ineffectiveness. Patients with low PD-L1 expression also have a better response to immunotherapy. Therefore, the combination of immunotherapy and chemotherapy drugs may improve the treatment effectiveness of patients.

Existing research shows that NSCLC's new adjuvant immunotherapy has good clinical effect, but because the immune checkpoint inhibitor improves the activity of T lymphocytes, which may damage the normal Immune tolerance, the immune system may damage normal tissues, resulting in the occurrence of immune related adverse events (IRAE) [18,19]. Common immune related adverse events mainly include toxicity that occurs in the skin, endocrine system, lungs, liver, digestive tract, etc. Rare adverse events mainly include toxicity that occurs in the heart, kidneys, blood, etc. In this study, 89 patients experienced varying degrees of treatment-related adverse reactions, with nausea being the most common adverse reaction. Most patients were classified as Grade 1, while a few Grade 2 patients followed medical advice to use antiemetic drugs. Among all the adverse reactions, the clinical manifestations were mainly decreased appetite, nausea and general fatigue, and laboratory examinations were mainly Hypoalbuminemia and increased Alanine transaminase, which were basically consistent with the results of relevant domestic studies [8]. There are fewer patients with moderate and severe adverse reactions, a total of 25 cases. Among them, 6 patients with grade 3 and 3 patients with grade 4 had decreased neutrophil count, and 6 patients with grade 3 Leukopenia, which is related to drug treatment, but both are within the controllable range. After chemotherapy, patients can be given drugs that promote leukopenia to reduce the incidence of adverse reactions.

In summary, PD-1/PD-L1 immunotherapy combined with neoadjuvant chemotherapy is beneficial for patients with NSCLC resection, can effectively eliminate tumor cells, and the adverse reactions are within an acceptable range. However, the sample size of this study is small, and large-scale clinical studies are needed for analysis in the later stage, as well as long-term efficacy analysis.

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