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Review Article

Neoadjuvant immunotherapy for resectable non-small cell lung cancer

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Abstract: Lung cancer is the malignant tumor with the highest morbidity and mortality in the world. In recent ten years, with the emergence of new drugs and the optimization of treatment mode, the treatment of lung cancer is entering an era of precision and individualization. Neoadjuvant therapy can reduce tumor size, degrade tumor stage, kill circulating tumor cells and micrometastases in the body, afford operation possibility, and benefit the long-term survival of patients. However, the traditional neoadjuvant chemotherapy combined with surgical treatment seems to have entered the bottleneck period of efficacy and is difficult to achieve breakthrough progress. At the same time, the amazing efficacy of immunotherapy is gradually innovating the treatment mode of lung cancer. In recent years, the research data of immune checkpoint inhibitors in the treatment of non-small cell lung cancer (NSCLC) shows an explosive growth. Immunotherapy has been applied to the first-line treatment of advanced NSCLC. Therefore, some clinical trials have applied immunotherapy to neoadjuvant treatment of resectable NSCLC patients. In this paper, the efficacy, possible mechanisms, potential risks and existing problems of neoadjuvant immunotherapy for resectable NSCLC patients are reviewed, and the future development direction of neoadjuvant immunotherapy is discussed.

Keywords: Neoadjuvant immunotherapy, non-small cell lung cancer, resectable, immune checkpoint inhibitors

Introduction

The incidence and mortality of lung cancer ranks first among malignant tumors. Among them, non-small cell lung cancer (NSCLC) accounts for about 85%, the number of patients is still increasing year by year. According to the latest data, there are about 2.09 million new lung cancer patients and 1.76 million deaths worldwide [1, 2].

So far, surgical treatment is still the most effective treatment strategy for resectable diseases [3]. However, even after complete tumor resection, the long-term survival of patients is not ideal. Postoperative recurrence is a thorny problem for patients with operable lung cancer in the early and middle stages. How to optimize the treatment strategy and prolong the survival of patients is a hot topic in the field of lung cancer. According to the International Association for the study of lung cancer staging (8th Edition) data, the 5-year survival rate of stage III NSCLC was less than 30%, while that of stage Ib NSCLC was only about 70% [4]. Perioperative treatment strategies still need to be optimized and improved.

Adjuvant chemotherapy and neoadjuvant chemotherapy have been widely used in the perioperative treatment of resectable NSCLC, neoadjuvant chemotherapy can improve the chance of radical resection by reducing tumor size, eliminating micrometastasis and reducing the risk of tumor recurrence [5, 6]. However, platinum based chemotherapy drugs can kill tumor cells, but also inevitably damage non tumor cells, the survival benefit of patients is not significantly improved, and the 5-year survival rate of patients after receiving neoadjuvant chemotherapy is only improved by about 5% [7-9].

Because of the great success of targeted therapy in patients with sensitive mutations, neoadjuvant targeted therapy has also been used in the perioperative treatment of NSCLC patients.

Studies have shown that neoadjuvant targeted therapy can reduce the risk of postoperative recurrence in these patients, and the resection rate is also higher than that of traditional neoadjuvant chemotherapy containing platinum, but no complete pathological response (PCR) has been observed [10, 11]. At the same time, there are limited treatments for patients with wild-type NSCLC, and the lack of data on neoadjuvant targeted therapy for stage I-II NSCLC, researchers are committed to exploring new treatment options.

The emergence of immune checkpoint inhibitors (ICIs) has changed the inherent treatment mode of advanced NSCLC. The progression free survival (PFS) and overall survival (OS) of patients have been significantly improved. Immunotherapy has moved from the second-line treatment of advanced lung cancer to the first-line treatment, and gradually extended to consolidation treatment of locally advanced lung cancer [12]. Whether used alone or in combination, ICIs have achieved significant efficacy in a variety of tumors, such as melanoma, Hodgkin's lymphoma, renal cell carcinoma and NSCLC [13, 14].

Compared with chemotherapy and targeted therapy, the target of immunotherapy is not the tumor cells themselves, mainly the immune microenvironment. Immunotherapy can improve the immunosuppressive microenvironment of tumor, activate the body's autoimmune system, and ultimately achieve the purpose of killing tumor. So in principle, immunotherapy is different from chemotherapy and targeted therapy. Therefore, once it takes effect, it will often achieve sustained curative effect [13, 15]. In the context of cancer immunotherapy, the therapeutic effect of checkpoint inhibitors in advanced NSCLC naturally leads to the research on the efficacy of these drugs in early cancer, including locally advanced NSCLC and even stage I tumor. Neoadjuvant immunotherapy may provide an additional advantage. Studies have shown that neoadjuvant immunotherapy can bring more significant overall survival benefits [16, 17]. In early resectable NSCLC, neoadjuvant immunotherapy can achieve 45% of the main pathological remission (MPR) [18]. The above results make the application prospect of neoadjuvant immunotherapy attracted much attention.

In this review, we will discuss the existing preclinical data and emerging clinical findings, which are related to the application of tumor immunotherapy in neoadjuvant therapy and its potential mechanism of action. We will also highlight the potential problems with the use of neoadjuvant immunotherapy.

Mechanism of neoadjuvant immunotherapy for NSCLC

Immunotherapy of tumor is to use immunological principles and methods, through activating immune cells in the body and enhancing the body's anti-tumor immune response, help the immune system to recognize and reacquire the ability of immune surveillance and immune attack on cancer cells, specifically remove small residual tumor lesions, inhibit tumor growth, and break the immune tolerance.

The researchers found that the proportion of regulatory T cells increased, while the proportion of natural killer cells and dendritic cells decreased, and the proportion of effector T cells/regulatory T cells decreased in tumor tissues after surgical resection [19].

Previous studies [20] also showed that the number of tumor infiltrating T cells was significantly positively correlated with prognosis, which provided evidence for the application of immunotherapy in neoadjuvant therapy of early tumors. Early stage tumor has strong host immune adaptability and low tumor clonal heterogeneity, which can be regarded as a special vaccine. Through ICIs, specific anti-tumor immune response can be activated and early immune memory can be established [21].

After primary tumor resection, specific tumor T cells can still maintain a stable state, eliminate potential metastatic lesions and improve the cure rate. In a preclinical study [22], different combined immunotherapies were used in two kinds of mouse models of breast cancer to observe the different curative effects of neoadjuvant therapy before primary tumor resection or adjuvant therapy after operation. The results showed that no matter what type of immunotherapy, neoadjuvant therapy had more advantages than adjuvant therapy in eliminating micrometastasis. At the molecular level, the number of tumor specific CD8+ lymphocytes in peripheral blood increased significantly after

neoadjuvant and adjuvant ICIs treatment. High levels of tumor specific CD8+ lymphocytes indicate a longer survival time. The possible mechanism is: after immunotherapy, the number of activated tumor specific CD8+ T cells increases, which can kill the primary tumor and metastatic lymph nodes. And it will lead to the release of new anti-tumor antigens. After primary tumor resection, the ratio of T cells/tumor cells in blood and micrometastasis sites was significantly increased, which may help to eliminate the residual tumor tissue. After tumor clearance, the number of tumor specific CD8+ T cells remained stable. Although it is uncertain whether this is necessary to maintain complete remission, it can be observed that the number of these cells remains stable in long-term survival mice after neoadjuvant immunotherapy. Other follow-up studies [23, 24] also confirmed the effectiveness of neoadjuvant immunotherapy in different mouse models.

Another widely accepted hypothesis is that the preoperative immune system of patients with early NSCLC is more complete, and the complete existence of early tumor has strong host immune characteristics, which can be stimulated to release more new tumor antigens, thus inducing more extensive and lasting anti-tumor effects [22, 25-27].

One explanation is that the primary tumor itself plays a key role in promoting the expansion/initiation of tumor specific T cells during treatment. The presence or absence of primary tumor is the only significant difference between adjuvant and neoadjuvant therapies. In addition, primary tumor may be the main source of tumor antigen and can enrich tumor specific T cells [14, 28].

Therefore, ICIs benefit from reducing tumor induced immunosuppression and increasing the anti-tumor effect of autoimmune system. These encouraging preclinical findings provide a powerful impetus for the clinical evaluation of neoadjuvant immunotherapy.

Clinical trials of neoadjuvant immunotherapy in NSCLC

CheckMate159

The earliest study of immunotherapy in the field of neoadjuvant therapy of NSCLC is CheckMate 159 [18]. A total of 21 untreated, surgically resectable patients with early stage (stage I, II, or IIIa) NSCLC were enrolled in this clinical trial. Two cycles of nivolumab were given preoperatively. Nivolumab (3 mg/kg) was administered intravenously every 2 weeks, and the operation was performed about 4 weeks after administration. The primary endpoint of the study was safety and feasibility. The secondary and exploratory endpoints were remission, PD-L1 expression, tumor mutation burden (TMB) and mutation associated antigen-specific T cell response.

In terms of the feasibility and safety of the primary study endpoint, 5 patients had immunotherapy related side effects, and the rest patients had no obvious adverse reactions. One patient died during the postoperative study, which was not related to the study drug (caused by traumatic fall). MPR was observed in 9 patients (45%). This proportion is almost twice of the previously reported MPR of neoadjuvant chemotherapy [29, 30].

In 21 patients, except for one patient who did not undergo surgery due to disease progression, the remaining 20 patients received surgical treatment, and there was no surgical delay due to neoadjuvant immunotherapy. 14 patients underwent thoracotomy and 6 patients underwent minimally invasive surgery. It is worth noting that most patients underwent thoracotomy rather than minimally invasive surgery. Studies have shown that it may be related to the late stage of patients (IIb-IIIa) and adhesion between tissues. But whether it is related to neoadjuvant immunotherapy needs further study [31]. Of the 20 resected patients, 16 had no recurrence one year after resection, and the median disease-free survival (DFS) and overall survival (OS) were not yet reached.

In this study, 21 patients were evaluated according to response evaluation criteria in solid tumors (RECIST). The results showed that there was no correlation between imaging findings and pathological reaction after treatment. Among them, 2 cases (10%) had partial remission (PR), 18 cases (86%) had stable disease (SD), and 1 case (5%) had disease progression. However, pathological examination after surgery found that 45% of the patients (9 cases) had MPR. The rest of the patients also had different degrees of pathological remission, half of the patients had tumor cell regression more

than 65%, 2 patients had PCR. The expression of PD-L1 was detected in 15 patients, the results showed that both PD-L1 positive and PD-L1 negative patients responded to nivolumab. 40% of the patients had pathological deterioration (8 cases). It can be seen that the number of T cells in tumor and peripheral blood increased significantly, and a large number of lymphocytes and macrophages infiltrated in the tumor, suggesting the activation of the immune system and tumor necrosis. Although MPR was observed in both PD-L1 positive and PD-L1 negative tumor patients, patients with higher TMB had a higher proportion of MPR [32]. Interestingly, there were 2 patients with tumor enlargement assessed by imaging (not up to the standard of disease progression), but pathological examination showed that MPR and PCR, and there were a large number of infiltrating T cells and macrophages in the tumor, which may be the cause of tumor enlargement.

The correlation between ctDNA and pathological partial remission (tumor load reduction ≥30%) indicated that ctDNA could be used as a potential biomarker to predict treatment response. The expansion and long-term maintenance of tumor specific T cells in peripheral blood in disease-free state indicate that tumor specific T cells can be used as potential biomarkers for predicting therapeutic response and long-term monitoring.

LCMC3 (NCT02927301)

LCMC3 [33, 34] is a single arm, open, multicenter phase II study to evaluate the efficacy and safety of atezolizumab in neoadjuvant immunotherapy for NSCLC with stage Ib-IIIb. The patients were given two cycles of neoadjuvant immunotherapy with atezolizumab (1200 mg, every 3 weeks), and surgery was performed in the sixth week.

As of September 2019, enrollment is completed, 180 cases are planned to be enrolled, 164 cases have been recruited. Data analysis of 101 patients showed that 95% of the patients completed two cycles of treatment, and the rest completed one cycle of treatment; 5 patients (5/101) lost the opportunity of surgery due to disease progression, and 89% of the patients completed surgery. Among the 90 patients who completed the operation, the DFS rate was 89%, and the DFS rates in stage Ib, stage II and stage III were 90%, 90% and 87% respectively. Preliminary biomarker data analysis showed that in patients with MPR induced by atezolizumab neoadjuvant therapy, the expansion of NK cells and granulocytes in peripheral blood, and the increase of dendritic cells and B cell subsets in lymph nodes were observed. This study also uses RECIST standard to evaluate the curative effect, showing a good therapeutic effect. Among them, 7% patients (6/90) had PR, and 89% patients (80/90) had SD. In terms of safety, only 6 of 101 patients had grade 3-4 treatment-related adverse events (TRAEs), and 2 patients had grade 5 non-TRAEs. In addition, LCMC3 study, as the only study to show patients with positive driving genes (EGFR, ALK), is also an important point. None of the 8 patients with positive driver gene obtained MPR, which indicated that these patients were not suitable for immunoneoadjuvant therapy. The study of markers is another focus, which did not find the correlation between PD-L1 staining intensity and pathological response, nor did it find the predictive value of TMB. In 40 cases of exon sequencing data of tumor gene mutation and MPR association analysis is also negative conclusion.

MK3475-223

MK3475-223 [35] is a one arm, phase I, dose escalation and extended cohort trial to investigate the safety and feasibility of neoadjuvant pembrolizumab in patients with early resectable NSCLC. The main objectives of this study were to determine the safety of pembrolizuma treatment, to establish the recommended dose for phase II, clinical trials, and to evaluate pathological and imaging responses. The study design was based on the classic 3×3 cohort, but the difference between the cohort was not the drug dose, but the number of preoperative pembrolizuma treatment (group 1 treated once, group 2 and group 3 treated twice, with an interval of 3 weeks). There were also differences in the interval between the last pembrolizuma treatment and surgical treatment in the three groups: 3 weeks in the first group, 2 weeks in the second group and 1 week in the third group. The therapeutic dose of pembrolizuma was 200 mg. Dose limiting toxicities (DLT) are defined as severe surgical complications (such as bleeding, delayed wound healing,

acute respiratory distress syndrome) or significant prolonged operation time. DLT evaluation period was defined as 30 days after operation.

According to the results updated in the American Society of Clinical Oncology (ASCO) in 2019 showed that a total of 15 patients received neoadjuvant therapy and 13 patients underwent surgery. Of the 10 patients who received 2 cycles of pembrolizumab, 4 achieved MPR (40%). Although all patients had no DLT, there were 2 cases of operation delay due to side effects of immunotherapy and 3 cases of TRAEs above grade 3. There was no correlation between pretreatment PD-L1 level and pathological remission, and no correlation between tumor volume and lymph node status and MPR. For all patients who achieved MPR, the relative interval from the first treatment to surgery was longer.

ChiCTR-OIC-17013726

ChiCTR-OIC-17013726 [36] is an open, single center, phase Ib study conducted in China to evaluate the efficacy of singtilimab monotherapy in neoadjuvant treatment of resectable NSCLC. The primary end point was safety. Efficacy end points included rate of MPR and objective response rate (ORR). A total of 40 NSCLC patients (32 male and 8 female) were included in this study, including 33 cases (82.5%) of squamous cell carcinoma and 7 cases of adenocarcinoma. They received two cycles of sintilimab treatment, and then 37 patients underwent radical resection after 4 weeks of observation. Among 37 patients, 15 (40.5%) achieved MPR, including 6 (16.2%) with PCR in primary tumor and 3 (8.1%) in lymph nodes as well. Compared with adenocarcinoma, squamous cell NSCLC showed better response (MPR: 0% vs 48.4%). A total of 21 patients (52.5%) experienced neoadjuvant TRAEs. 4 patients (10.0%) experienced grade 3 or higher neoadjuvant TRAEs, and 1 patient had grade 5 TRAEs. 8 patients achieved radiological partial response, resulting in an ORR of 20.0%. It is worth noting that PET-CT examination was performed in all patients before and after neoadjuvant therapy. Among the 8 patients whose maximum standard uptake value (SUV) of main lesion decreased by more than 30%, 5 patients achieved MPR (62.5%). The decrease of the maximum standardized uptake after sintilimab may predict the pathological response.

NADIM (NCT03081689)

In addition to the single drug model, researchers from Spain conducted the NADIM (NCT03081689) study to evaluate the feasibility, safety, antitumor activity and survival outcome of nivolumab combined with standard chemotherapy in neoadjuvant treatment of resectable stage IIIa NSCLC patients [37-39].

NADIM study is a phase II, single arm, open, multicenter study. Patients over 18 years old with stage IIIa NSCLC (N2 or T4N0-1) confirmed by histology or cytology and resectable with ECOG score of 0 or 1 were included in the study. Three cycles of neoadjuvant therapy (21 days as a cycle) were given before operation: chemotherapy (paclitaxel + carboplatin) + nivolumab (360 mg); 3-4 weeks later, the operation was performed. The patients were treated with nivolumab for 1 year after operation (240 mg/2 weeks for 4 months; 480 mg/4 weeks for 8 months). The primary end point was 24 month PFS in the modified intention to treat (ITT) population (ITTP: including all patients receiving neoadjuvant therapy) and the protocol compliant population (PPP: including all patients receiving tumor resection and receiving at least one cycle of nivolumab adjuvant therapy).

From April 26, 2017 to August 25, 2018, 51 patients met the inclusion criteria. Finally, 46 patients were included and received neoadjuvant therapy, so they were included in ITTP. Among the 46 patients, 41 (89%) received surgical treatment, and all patients achieved complete tumor resection. Of the 41 patients who underwent surgery, 37 (90%) received at least one cycle of nivolumab adjuvant therapy.

As of January 31, 2020, the median duration of follow-up was 24 months, 35/41 patients (85%) were still alive or had no recurrence, and the median OS was not reached in ITTP or PPP. In ITTP, the 12 month PFS rate was 95.7%, the 18 month PFS rate was 87%, and the 24 month PFS rate was 77.1%. In PPP, the 12 month, 18 month, and 24 month PFS rates were 100%, 91.9%, and 87.9%, respectively. Among the patients who received nivolumab adjuvant therapy, 89% had no recurrence related symptoms.

43/46 patients (93%) had TRAEs during neoadjuvant therapy. The most common TRAEs were weakness or fatigue, alopecia, nausea and neurotoxicity; TRAEs above grade 3 were lipase elevation (7%) and febrile neutropenia (7%); TRAEs during neoadjuvant therapy did not lead to treatment interruption, dose reduction, operation delay or death; 3 patients (7%) were unable to receive nivolumab adjuvant therapy due to TRAEs (2 due to hematologic toxicity and 1 due to renal insufficiency).

Based on RECIST 1.1 criteria, 76% of the patients had ORR, of which 4% were evaluated as complete response (CR), 72% as PR, 24% as SD and none as progressive disease (PD); MPR rate was 83%. 63% of the patients achieved PCR. 33% and 73% of patients with SD or PR evaluated by imaging respectively, which were confirmed as PCR. There was no correlation between clinicopathological characteristics and pathological remission rate.

In this study, patients who received neoadjuvant immunotherapy combined with chemotherapy (neoadjuvant chemoimmunotherapy) received surgery in time, and did not withdraw from the study because of disease progression or toxicity. At present, a number of phase III clinical trials are being carried out: KEYNOTE-671, CheckMate 816, CheckMate 77T, IMpower 030 (see **Table 1**). These studies will further reveal the clinical effect of neoadjuvant immunotherapy combined with chemotherapy and its prospect in neoadjuvant therapy in the future.

The values of PCR and MPR in NADIM study were significantly higher than those in CheckMate159 study, suggesting that neoadjuvant immunotherapy combined with chemotherapy may bring better efficacy. Perhaps locally advanced lung cancer can be promoted to a curable disease.

NCT02716038

NCT02716038 study [40] is an open label, multicenter, single arm, phase II clinical study to evaluate whether neoadjuvant chemotherapy combined with atezolizumab can increase the benefit of patients. The primary endpoint was MPR. A total of 30 patients were recruited, 29 patients underwent surgery, and 26 patients underwent R0 resection successfully. 12 patients (46%) underwent video-assisted thoracoscopic surgery and 14 patients (54%) underwent thoracotomy. There were no treatment-related surgical delay and complications caused by neoadjuvant therapy. Of the 30 patients, 17 (57%) achieved MPR and 10 (33%) achieved PCR. No significant associations between MPR or PCR and pretreatment PD-L1 expression. As of August 7, 2019, the median follow-up period was 12.9 months. Among the 26 patients who successfully underwent R0 resection, 19 (73%) survived and were disease-free. Among the 30 patients, 9 (30%) recurred and 2 (7%) were suspected of disease progression during treatment. All of the 4 patients (13%) who did not undergo surgical resection had recurrence or progression of the disease. The most common treatment-related grade 3-4 adverse events were neutropenia (50%), elevated alanine aminotransferase (7%), elevated aspartate aminotransferase (7%) and thrombocytopenia (7%). 7 TRAEs included 1 case of grade 3 febrile neutropenia, 1 case of grade 4 hyperglycemia, and 1 case of grade 2 bronchopulmonary hemorrhage. There was no treatment-related death. At present, most of the trials of neoadjuvant immunotherapy combined with chemotherapy give patients additional ICIs adjuvant treatment for one year after operation, and this trial only implements neoadjuvant treatment for patients. For patients with MPR, whether postoperative adjuvant therapy is needed is a research topic in the future.

NEOSTAR (NCT03158129)

In addition to neoadjuvant monotherapy or neoadjuvant chemoimmunotherapy, dual immunotherapy for neoadjuvant therapy is also a way of thinking. NEOSTAR (NCT03158129) is a study to evaluate the effect of neoadjuvant therapy with nivolumab or nivolumab combined with CTLA4 inhibitor ipilimumab in patients with resectable NSCLC. A total of 44 patients with stage I-IIIa resectable NSCLC (PS 0-1 point) were randomly divided into two groups. They were treated with nivolumab (N group, 23 cases) or nivolumab + ipilimumab (NI group, 21 cases) respectively. The primary end point was MPR. In the total population, the rate of MPR and PCR of NI group were 33%, which was better than 17% of N group. In this study, 39 patients (89%) were successfully operated after neoadjuvant therapy, 22 were in group N

Table 1. Ongoing neoadjuvant ICIs trials prior to surgery in resectable NSCLC

Trial	Start date	Phase	Stage	Neoadjuvant intervention	Target enroll	Primary end point (s)
NCT02994576 (PRINCEPS)	2016	II	Ib; II; IIIa	Atezolizumab	60	Toxicities or morbidities
NCT02927301 (LCMC3)	2017	II	Ib; II; IIIa; selected IIIb	Atezolizumab	180	MPR
MK3475-223	2017	I	I; II	Pembrolizumab	28	DLT
NCT02818920 (TOP1501)	2017	II	Ib; II; IIIa	Pembrolizumab	35	Surgical Feasibility
NCT03197467 (NEOMUN)	2018	II	II; IIIa	Pembrolizumab	30	Safety
NCT03732664	2018	I	I; II; IIIa	Nivolumab	40	Safety; AEs
NCT03081689 (NADIM)	2017	II	IIIa	Nivolumab + platinum doublet	46	PFS
NCT03800134 (AEGEAN)	2018	III	II; III	Durvalumab + platinum doublet	800	MPR; EFS
NCT03456063 (IMpower030)	2018	III	II; IIIa; selected IIIb	Atezolizumab + platinum doublet	450	MPR; EFS
NCT03425643 (KEYNOTE671)	2018	III	II; IIIa; selected IIIb	Pembrolizumab + platinum doublet	786	EFS;OS
NCT04025879	2019	III	II; IIIa; IIIb	Chemotherapy + nivolumab	452	EFS
NCT02998528 (CheckMate 816)	2016	III	Ib; II; IIIa	Nivolumab ± ipilimumab	350	EFS; PCR
NCT03158129 (NEOSTAR)	2017	II	I; II; IIIa	Nivolumab ± ipilimumab	88	MPR
NCT03237377	2017	II	IIIa	Durvalumab + radiation	32	Safety

OS: overall survival; PFS: progression-free survival; MPR: major pathologic responses; AEs: advent events; PCR: complete pathological response; EFS: event-free survival; DLT: dose limiting toxicities.

and 17 in group NI. Among the 5 patients who did not receive surgery, 1 patient in NI group and 1 patient in N group was excluded because of violating the treatment plan, and the other 3 patients failed to complete neoadjuvant therapy due to serious side effects. 1 patient in group N developed grade 3 hypoxia, 2 patients in group NI developed grade 3 diarrhea, and 1 patient developed grade 2 pneumonia [41, 42].

27 patients (73%) underwent thoracotomy, 7 patients (19%) underwent thoracoscopic pneumonectomy, and 3 patients (8%) underwent robot assisted pneumonectomy. 40% of the surgeons think that the operation is more difficult after neoadjuvant immunotherapy. Postoperative complications included 2 cases of endobronchial pleural fistula and 8 cases of pneumothorax. 6 patients had grade 3-5 TRAEs, including 4 cases in group N and 2 cases in group NI [43]. In general, the combination therapy may be more effective, but it may face more toxic and side effects.

In the study of CheckMate159 [18], Forde PM and other scholars found that neoadjuvant immunotherapy in resectable NSCLC is safe and feasible, and the pathological response rate is encouraging. And based on the excellent data of nivolumab combined with ipilimumab in the treatment of advanced NSCLC [44]. A further study was conducted to evaluate the efficacy of nivolumab combined with ipilimumab in the treatment of resectable NSCLC (NCT02259621) [45]. The study plans to recruit 15 NSCLC patients with resectable Ib-IIIa, neoadjuvant immunotherapy was given 6 weeks before surgery. The primary endpoint was safety and feasibility, and the secondary endpoint was pathological response. Among the 9 recruited patients, all were treated according to the original plan before operation, but 6 of the 9 patients had TRAEs, of which 3 patients (33%) had grade 3 or above adverse events, including acute respiratory distress syndrome (ARDS, grade 5), pneumonia, rash, pruritus and headache. 3 of the 9 patients had biopsy confirmed tumor progression and could not undergo final surgery. 6 patients finally received surgical treatment, among them, 3 cases survived and were disease-free, 2 cases recurred and received systemic treatment actively, and 1 case died of ARDS. Pathological response was significantly correlated with pretreatment PD-L1 expression, but not with TMB. Although the treatment was feasible, the study was terminated early because of the high toxicity (higher than the interim report data of NEOSTAR study, and the experimental study of neoadjuvant immunotherapy and neoadjuvant chemoimmunotherapy), and several cases of primary tumor progression leading to the failure of final resection. Perhaps, dual immunotherapy for neoadjuvant therapy (Neoadjuvant nivolumab plus ipilimumab) is not a good choice.

Problems to be solved in neoadjuvant immunotherapy for resectable NSCLC

Side effects of neoadjuvant immunotherapy

Although immunotherapy has good curative effect, the evaluation of a treatment method is not only depends on the curative effect, but

also on the safety. Because the mechanism of immunotherapy is different from traditional chemotherapy and targeted therapy, it has its own unique toxic and side effects, particularly those used in combinations, might interfere with potentially curative surgery. The mechanism of ICIs is to block the binding of PD-L1 and PD-1 and reactivate T cells to restore the tumor killing effect of T cells. But once activated, T cells will not only attack cancer cells in vivo, but also damage normal tissue cells. Due to the imbalance of the immune system, there are many adverse reactions, which are called immune related adverse events (irAEs). Some people call immunotherapy a double-edged sword. Therefore, we need to improve the clinical understanding, diagnosis and management of these side effects [46, 47].

There are four characteristics of irAEs [46-49]: (1) It can involve multiple organs. The occurrence of immune related toxicity is related to the change of the function of the body's autoimmune system. This kind of side effect can affect almost all organ functions of the whole body. The main toxicity will focus on some immune related organs, such as intestine, skin, thyroid and liver. The attack of these organs is not related to time, but related to the function of each organ itself. Its functional recovery is different. Therefore, its performance is completely different from the toxicity of chemotherapy. (2) The tolerance of immunotherapy is better than chemotherapy, and the overall incidence of adverse reactions is lower than chemotherapy, but the duration may be longer. Among the NSCLC patients receiving ICIs, 7%-13% of them have grade 3 or higher irAEs. In all types of cancer patients treated with ICIs, the incidence of high-grade irAEs was less than 20%. (3) Most of the immunotoxicity is reversible. (4) Severe irAEs can be life-threatening. Although the incidence of immunotherapy related side effects is low, ICIs may lead to serious side effects. An evaluation study of fatal side effects of ICIs showed that the mortality rate of patients treated with ICIs was 0.6% [50].

However, it can be seen from the overall data that, except for the high rate of grade 3/4 irAEs in NCT02716038 study, the grade 3/4 adverse reactions in other neoadjuvant immunotherapy studies are not high. Most patients can receive surgical treatment after receiving neoadjuvant immunotherapy. Even if there are drug-related adverse reactions, most symptoms can be alleviated by treatment without significant surgical delay or cancellation. irAEs need the comprehensive management of multi disciplinary team (MDT) to formulate individualized treatment plan, so that patients can obtain clinical benefits and minimize side effects. In short, clinicians should be vigilant, not only pay attention to the anti-tumor efficacy, but also pay attention to the adverse reactions, master the common types, classification, diagnosis and treatment management methods of adverse reactions, achieve early diagnosis and early treatment, control the adverse reactions at a low level, reduce the risk and improve the prognosis.

Efficacy prediction and benefit population of neoadjuvant immunotherapy

Although ICIs have achieved gratifying results in NSCLC, there are still no satisfactory biomarkers to screen the best beneift population. How to screen out the benefit population and find good markers to predict the curative effect is a problem to be solved.

At present, clinical trials have confirmed that the main biomarkers of ICIs are tumor PD-L1 expression level [51] and TMB [52], but its application in lung cancer remains to be further confirmed. Study [51] showed that ICIs may be effective when the expression of PD-L1 in tumors is high. However, in CheckMate159 study, 45% of patients who achieved MPR had no correlation with the expression level of PD-L1. LCMC3 and NEOSTAR studies also showed that treatment response could be observed in both PD-L1 positive and PD-L1 negative tumors. The results of the CheckMate159 study showed that patients who achieved MPR had higher TMB than those who did not. Another study (NCT02259621) conducted by the same research team came to the opposite conclusion. In the LCMC3 study, TMB was not correlated with whether or not to achieve MPR. NEOSTAR study showed that patients with MPR had higher pretreatment PD-L1 expression, and patients with PD-L1>1% had less residual tumor after treatment. Patients with higher pretreatment PD-L1 expression may obtain more anti-tumor effect. MK3475-223 study did not observe the corre-

lation between PD-L1 expression and MPR. NCT02716038 study suggested that patients can benefit from neoadjuvant immunotherapy regardless of PD-L1 expression level.

In addition, the response rate of PD-1 pathway blocking was lower in NSCLC with positive driving genes (EGFR, ALK) [53, 54]. Researchers suggest that EGFR gene mutation can regulate the activation of PD-1 pathway and reduce the expression of PD-L1 [55]. Some co-mutations, such as KRAS and STK11, may lead to poor immunotherapy effect [56]. NCT02716038 and other studies draw similar conclusions. The frequency of STK11/KEAP1 co-mutation in metastatic lung adenocarcinoma is twice than that in resectable lung adenocarcinoma, suggesting that this molecular structure may be an indicator of invasiveness [57].

Although the results of different studies are inconsistent, some even contradict each other, the biomarkers predicting the efficacy of immunotherapy are worthy of further study. It is still an urgent problem to explore more accurate predictive markers than PD-L1 and TMB, so as to accurately select the people who benefit from neoadjuvant immunotherapy and formulate personalized treatment plan.

Evaluation of curative effect and timing of operation in neoadjuvant immunotherapy

The clinical efficacy of immunotherapy lasted for a long time, and there were many response modes, mainly including delayed response, pseudoprogression and hyperprogression. How to accurately evaluate the clinical condition of patients and make a reasonable choice is a problem worthy of study. In the CheckMate 159 trial [18, 31, 32], the PR rate assessed by imaging was 10% (2/21), while the MPR assessed by pathology was about 45% (9/21); in one patient, the preoperative imaging evaluation showed that the tumor size was reduced by 35%, and the postoperative pathological evaluation showed that the pathological remission of the primary tumor was 100%, except for the residual tumor cells in the lymph nodes; in another patient, after two cycles of nivolumab treatment, pathology showed that the tumor shrank by 90%, while imaging images showed that the primary tumor became larger. This is a typical example of pseudoprogression caused by immunotherapy. It suggests that after immunotherapy, a large number of immune cells infiltrated into the tumor, resulting in the increase of imaging tumor lesions. Patients with pseudoprogression can still benefit from subsequent immunotherapy to achieve pathological remission [58]. Corresponding to pseudoprogression is hyperprogression, that is, the disease worsens rapidly after immunotherapy, and the growth rate of tumor is significantly faster or the clinical symptoms are significantly worse than before treatment [59]. Patients with hyperprogression are not suitable for immunotherapy. When resectable NSCLC patients show progress on imaging, if pseudoprogression and hyperprogression can not be identified in time, misdiagnosis may lead to delayed operation time, and even cause some patients to lose the opportunity of surgical treatment. Therefore, in the clinical practice of neoadjuvant immunotherapy, it is of great significance for researchers and clinicians to effectively identify pseudoprogression and hyperprogression and understand their pathological characteristics to prevent surgical delay. Some researchers have proposed immune related response evaluation criteria in solid tumors (irRECIST) [60]. Whether irRECIST can be used to evaluate the efficacy of neoadjuvant immunotherapy is worthy of further study.

Some scholars [61] found that the time of preoperative immunotherapy can affect the survival of tumor bearing mice. Too long or too short preoperative immunotherapy will affect the curative effect. At present, most of the research designs adopt 2-4 cycles of neoadjuvant therapy, and the time of neoadjuvant therapy is generally not more than 4 cycles. For example, in the CheckMate159 trial, patients received two cycles of neoadjuvant therapy; in the NADIM trial, patients received three cycles of neoadjuvant therapy; and in the NCT02716038 trial, participants received four cycles of immunotherapy. For practical reasons, the International Neoadjuvant Melanoma Consortium (INMC) suggests that the neoadjuvant therapy should be 6-8 weeks [62]. Distant metastasis or disease progression during neoadjuvant immunotherapy is a risk for patients. Two retrospective studies [63, 64] assessed the impact of delayed surgery for resectable NSCLC. There are few studies on the timing of surgery after neoadjuvant immunotherapy. How many times to use immunotherapy as neo-

adjuvant therapy and the most appropriate drug dose, and how long to stop the drug for surgery are the specific problems of clinical practice, which need more exploration and research.

Study endpoint setting

Since the 1990s, most clinical studies take OS as the main end point. The definition of OS is very clear, and it is also the gold standard reflecting the long-term survival of patients. With the continuous enrichment of treatment methods, the OS of lung cancer patients is also getting longer and longer. However, the clinical trials of resectable NSCLC with OS as the primary end point will take five years or even longer to complete, which greatly increases the cost of drug research and development and the difficulty of experimental innovation, there are certain constraints for the marketing of some effective drugs. In recent years, molecular targeted therapy, antiangiogenic therapy and immunotherapy for lung cancer have developed rapidly. In this case, some new requirements have been put forward for the design of clinical trials and research endpoints. This is especially true for immunotherapy, because once immunotherapy takes effect, there will be a lasting response, which can achieve lasting tumor clearance and clinical benefits. In practical work, it is more difficult to design the endpoint of immunotherapy clinical research. Previous studies of neoadjuvant chemotherapy [65] found that MPR had a good correlation with the long-term prognosis of lung cancer patients, and a report [9] suggested that MPR should be used as the end point of neoadjuvant chemotherapy. Therefore, MPR and PCR were selected as the primary or secondary endpoints in some phase II and III trials, but their accuracy still needs to be tested by long-term survival data. There is still no prospective phase III clinical controlled trial to confirm the correlation between MPR as the end point of clinical study and long-term survival of patients, and whether the conclusion of MPR in neoadjuvant chemotherapy can be applied to neoadjuvant immunotherapy is still uncertain. However, at present, although MPR can not be a particularly good clinical alternative research end point, in the new era of adjuvant immunotherapy, to some extent, it can observe the pathological relief of this special treatment, so as to further guide the follow-up treatment.

Summary and prospect

With the advent of the era of immunotherapy, immunotherapy is not limited to patients with advanced inoperable lung cancer. ICIs have been approved for advanced NSCLC, and have achieved better efficacy and safety than chemotherapy in a number of randomized controlled trials. At present, some scholars are exploring whether this benefit can be extended to early NSCLC. Although important clinical trials are still in progress, a series of data that have been completed and are in progress show that neoadjuvant immunotherapy has very good benefit potential. Patients can achieve obvious pathological remission, good tolerance and will not affect the operation. Neoadjuvant immunotherapy is a promising therapeutic strategy for patients with early resectable lung cancer. More phase III randomized controlled trials are expected to further confirm the effect of ICIs in neoadjuvant treatment of lung cancer.

Although many clinical studies have shown that neoadjuvant immunotherapy is safe and effective, there are still many details to be solved. Almost all the studies of neoadjuvant immunotherapy are exploratory, the sample size is small, the research results are not stable enough, easily affected by various factors, the research results are sometimes difficult to reproduce. Compared with a number of large-scale, prospective and long-term follow-up studies of immunotherapy in patients with advanced lung cancer, the relatively small sample, exploratory and short-term follow-up data of neoadjuvant immunotherapy need to be further demonstrated.

And what is the best model of neoadjuvant immunotherapy? Although the safety of immunomonotherapy was good, the MPR was low. In this study of CheckMate 159, the MPR of nivolumab neoadjuvant therapy reached 45%, but the follow-up studies failed to repeat this data. The MPR of dual immunotherapy for neoadjuvant therapy (Neoadjuvant nivolumab plus ipilimumab) is higher, however, due to more side effects and lower chance of subsequent surgery, the future application prospect of this treatment strategy is very uncertain. According to the current clinical research data, the efficacy of PD-1 inhibitor combined with chemotherapy (neoadjuvant chemoimmunotherapy) is bet-

ter than that of PD-1 monotherapy and dual immunotherapy for neoadjuvant therapy. In the NADIM study, MPR can reach 83%, but it should be noted that this is a small sample study, this still needs more clinical research data to verify.

For the evaluation of the curative effect of neoadjuvant immunotherapy, the generally accepted evaluation criteria are MPR and PCR of tumor tissue after surgery. Most clinical studies of neoadjuvant immunotherapy also evaluate the curative effect on this basis. However, this evaluation method can only evaluate the efficacy of neoadjuvant immunotherapy, but it still can not provide the basis for the postoperative efficacy and long-term disease monitoring. The long-term follow-up of patients after surgery lacks an accurate and reliable biomarker. Once patients have local recurrence or distant metastasis, they still rely on imaging examination as an auxiliary means, which makes it very difficult to detect the recurrence of lung cancer early. However, the immune response induced by neoadjuvant immunotherapy often makes the CT and other imaging evaluation results inconsistent with the degree of pathological remission. Some studies have developed immune related pathological remission criteria (irPRC) [66] to evaluate the efficacy of neoadjuvant immunotherapy, and have achieved stable results in clinical trials. However, more clinical evidence is still needed whether it can be promoted in the future.

What is the best cycle of neoadjuvant therapy? Most of the cycles of neoadjuvant immunotherapy are set at 2-4 cycles. Such treatment duration is not supported by evidence-based medicine, but more based on the data of neoadjuvant chemotherapy.

In addition, other key questions also need to be answered, including the best drug regimen, timing of surgical treatment, and whether additional adjuvant treatment is needed. Similarly, for patients with locally advanced disease (N2), in this case, the role of preoperative or postoperative radiotherapy remains to be explored. In the current and future trials, the active participation of surgeons will be the key to determine the best treatment strategy [67]. When using immune drugs, different kinds of drugs, dosage, frequency and route of administration may produce different curative effects. Therefore, although neoadjuvant immunotherapy is promising in the treatment of early lung cancer, our research on neoadjuvant immunotherapy is just beginning, and there are still a lot of concerns about the inflammatory mechanism of these drugs and the technical challenges they may bring during surgery, as well as drug side effects, such as pneumonia and endocrine diseases, which may cause problems after surgery, so we need to screen out the high benefit people to be included in our neoadjuvant immunotherapy, and at the same time, we need to screen out those patients with high recurrence risk or those who are easy to cause super progression, so as to make our treatment more accurate. The current clinical studies and more phase III trials will also explore these problems in a deeper level, and provide the basis for the rational and standardized application of neoadjuvant immunotherapy. There is still a long way to go.

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Disclosure of conflict of interest

None.

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