Short-term outcomes of neoadjuvant sintilimab with chemotherapy in stage III non-small cell lung cancer: a case series

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Background: Neoadjuvant chemoimmunotherapy seems to be a promising treatment option for stage III non-small cell lung cancer (NSCLC). Sintilimab, as a programmed death receptor-1 inhibitor, has exhibited a fine performance in treating NSCLC. However, the efficiency of sintilimab combined with chemotherapy for stage IIIA/IIIB NSCLC remains inconclusive. The purpose of this study was to share our experience on sintilimab in neoadjuvant chemoimmunotherapy for stage III NSCLC.

Methods: This study retrospectively reviewed patients who received surgical resection following 1–3 cycles of neoadjuvant sintilimab (200 mg) with chemotherapy for stage III NSCLC between June 2020 and March 2022 in our center. Patients characteristics, surgical factors, surgery-related complications 30 days postoperatively, and treatment-related adverse events (TRAEs) before surgery were recorded through reviewing medical record data and telephone follow-up.

Results: A total of eight patients were enrolled, including six cases of squamous cell carcinoma and two cases of adenocarcinoma. All of the patients received 1–3 cycles of neoadjuvant therapy. There were no treatment-related surgical delays. All patients underwent lobectomy, among which two underwent sleeve lobectomy and one received bronchoplasty. Five patients underwent open thoracotomy. Fibrosis of the primary tumor and lymph nodes was observed in all the cases. There were no surgery-related complications > grade 2 at 30 days postoperatively. According to the radiographic findings, one patient had stable disease and all of the others achieved a partial response. The median of maximum standardized uptake value change from baseline was a 52.75% reduction (range, 37.2–68.8%). Five patients achieved a major pathological response. R0 resection was achieved in all eight cases. One grade 4 event was observed. Neutropenia was the most common TRAE > grade 2 (3/8). There were no cases of treatment discontinuation or dose reduction due to TRAEs.

Conclusions: The current study found that neoadjuvant sintilimab plus chemotherapy bring a high rate of major pathological response and acceptable TRAEs. Even though it increased the difficulties of surgery, there is still no evidence suggesting that it will brings additional surgical death. We believe that neoadjuvant sintilimab plus chemotherapy might be feasible for stage III NSCLC.

Keywords: Neoadjuvant; non-small cell lung cancer (NSCLC); programmed cell death 1 inhibitor (PD-1 inhibitor); sintilimab; case series
Introduction

Stage III non-small cell lung cancer (NSCLC) accounts for approximately 40% of newly diagnosed NSCLC cases (1). Due to the specificity of lymph node metastasis, there are considerable differences in the clinical treatment and prognosis of stage III NSCLC. It is difficult to achieve ideal treatment outcomes by only relying on surgery since there is a high risk of recurrence and metastasis postoperatively (2). Numerous studies have confirmed the effectiveness of neoadjuvant therapy in the treatment of stage III NSCLC (3). However, most of the previous neoadjuvant regimens for stage III NSCLC involved chemotherapy or chemoradiotherapy (3); a considerable portion of patients are not sensitive to chemotherapy or combined chemoradiotherapy, and some patients even suffered disease progression.

Recently, several studies preliminary reported the safety and effectiveness of neoadjuvant chemoimmunotherapy for stage III NSCLC (4-6). One study reported that atezolizumab [a programmed cell death 1 ligand 1 (PD-L1) inhibitor] plus chemotherapy before surgery may be feasible for resectable stage IB–IIIA NSCLC (7). Furthermore, a phase 2 trial supported the potential value of the neoadjuvant nivolumab with chemotherapy for the treatment of resectable stage IIIA NSCLC (8). Similarly, a phase 2 trial from China suggested a neoadjuvant chemoimmunotherapy regimen for stage IIIA NSCLC and T3–4N2 IIIB NSCLC (9). Some other studies that explore the efficiency of the neoadjuvant chemoimmunotherapy on stage IIIA/B NSCLC are ongoing (10). However, there is currently no definitive conclusion on the feasibility of neoadjuvant chemoimmunotherapy for stage III NSCLC (5,6,11,12).

Sintilimab, as a PD-1 inhibitor from China, is reportedly tolerable for patients and has achieved a 40.5% major pathological response (MPR) rate in neoadjuvant therapy for stage IA–IIIB NSCLC (13). Recently, two phase 2 trials reported its safety and feasibility when combined with chemotherapy for resectable stage IIIA/IIIB NSCLC (14,15). However, the number of cases enrolled in these two studies was small and more cases are essential to better identify the efficiency of sintilimab combined with on stage III NSCLC. In this study, we similarly shared our experience on sintilimab in neoadjuvant chemoimmunotherapy for stage III NSCLC. We present the following article in accordance with the STROBE and AME Case Series reporting checklists (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1194/rc).

Methods

Study design

This is a single-center clinical retrospective study conducted in the Sixth Medical Center of Chinese PLA General Hospital. All consecutive stage III NSCLC patients who received surgery after neoadjuvant chemoimmunotherapy between June 2020 and March 2022 were screened. Patients were enrolled according to the following criteria: (I) those with pathologically confirmed clinical IIIa–IIIc NSCLC at the time of diagnosis (5,16); (II) cases in which neoadjuvant sintilimab plus chemotherapy was administered; and (III) patients lacking positive mutation of the corresponding driven-gene for lung adenocarcinoma (AD). Patients receiving only neoadjuvant immunotherapy were not included. This retrospective study was approved by the medical ethics committee of the Sixth Medical Center of Chinese PLA General Hospital (No. HZKY-PJ-2022-9), and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The informed consent for this retrospective research was waived.

Data collection

The patients’ clinical data, including gender, age, neoadjuvant chemoimmunotherapy strategy, clinical stage at diagnosis and post neoadjuvant chemoimmunotherapy, surgical procedure, intra-operative blood loss, interval between neoadjuvant chemoimmunotherapy and surgery, operation time, complications, intensive care unit (ICU) stay, and final pathological diagnosis, were collected by reviewing the medical record. Mortality and surgery-related complications ≥ grade 2 according to the Clavien-Dindo classification system were recorded for 30 days after surgery (17). Pulmonary air leakage is defined as air...
leak that persists for more than 5 days postoperatively. Neoadjuvant chemoimmunotherapy-related adverse events (treatment-related adverse events (TRAEs)) before surgery that occurred in more than two cases or were > grade 2 were recorded here. TRAEs were measured according to the National Cancer Institute Common Terminology Criteria for Adverse Eversion 5.0 (CTCAE5.0) (18). Telephone follow-up was performed per 3 weeks during the entire treatment period. All of the operations were performed by WA Song and TQ Gong (the corresponding authors), who are highly experienced thoracic surgeons.

**Radiographic and pathological assessment**

A radiographic positron emission tomography (PET)-computed tomography (CT) or CT was performed before surgery to analyze the radiographic response according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 (19). Pathological analysis was performed by a pathologist according to the Cottrell methods. Briefly, tumor samples <6 cm were analyzed entirely; however, for those >6 cm, more than one section/cm from the maximum dimension was analyzed. MPR was defined as ≤10% of viable residual tumor in samples (20).

### Statistical analysis

Data processing was carried out using SPSS 21.0 (IBM Corp., Armonk, NY, USA). Descriptive analysis was performed using statistics including the median with range, specific value, and frequency with percentage.

### Results

#### Patients characteristics

The characteristics of the enrolled patients are listed in Table 1. Nine patients who received neoadjuvant chemoimmunotherapy were screened between July 2020 and March 2022, and eight patients were eventually enrolled. One patient was excluded because of an indefinite pathological type. None of the included patients refused surgery after neoadjuvant treatment.

The included cohort comprised one female and seven males, with a median age of 66 years (range, 40–77 years). Six patients had squamous cell carcinoma (SCC) and two had AD. Five patients were stage IIIb, two were stage IIIa, and one was stage IIIc at the time of diagnosis. The neoadjuvant chemotherapy regimens for SCC and AD were paclitaxel plus platinum and pemetrexed.

| Case | Gender | Age, years | Histology | c-stage | PD-L1 TPS | Neoadjuvant chemoimmunotherapy regimen |
|------|--------|------------|-----------|---------|-----------|---------------------------------------|
| 1    | Male   | 63         | SCC       | T3N2M0, IIIb | –         | Albumin-bound paclitaxel 400 g d1 + cisplatin 60 mg d1–d2 + sintilimab 200 mg d2, 2 cycles |
| 2    | Male   | 77         | SCC       | T4N2M0, IIIb | –         | Albumin-bound paclitaxel 300 g d1 + carboplatin 60 mg d1 + sintilimab 200 mg d2, 2 cycles |
| 3    | Female | 40         | SCC       | T4N3M0, IIic | –         | Albumin-bound paclitaxel 300 g d1 + cisplatin 60 mg d1, 30 mg d2–d3 + sintilimab 200 mg d3, 3 cycles |
| 4    | Male   | 72         | SCC       | T3N2M0, IIIb | –         | Paclitaxel liposome 240 mg d1 + cisplatin 120 mg d1 + sintilimab 200 mg d2, 2 cycles |
| 5    | Male   | 70         | SCC       | T2bN2M0, IIIb | –         | Albumin-bound paclitaxel 400 g d1 + cisplatin 30 mg d1–d3 + sintilimab 200 mg d5, 1 cycle |
| 6    | Male   | 65         | SCC       | T3N2M0, IIIb | –         | Paclitaxel liposome 210 mg d1 + cisplatin 60 mg d1–d2 + sintilimab 200 mg d2, 2 cycles |
| 7    | Male   | 65         | AD        | T4N2M0, IIIb | <1%       | Pemetrexed disodium 0.8 g d1 + lobaplatin 50 mg d1 + sintilimab 200 mg d2, 2 cycles |
| 8    | Male   | 67         | AD        | T1bN2M0, IIIa | 90%      | Pemetrexed disodium 0.95 g d1 + cisplatin 50 mg d1–d3 + sintilimab 200 mg d2, 2 cycles |

*, c-stage, clinical stage at the time of first diagnosis, according to the 8th edition of TNM staging system. –, not detected; AD, adenocarcinoma; PD-L1, programmed cell death ligand 1; SCC, squamous cell carcinoma; TNM, tumor node metastasis; TPS, tissue polypeptide specific antigen.
plus platinum, respectively. All of the patients received 1–3 cycles. Radiological assessment was performed following the completion of neoadjuvant chemotherapy. The PD-L1 tissue polypeptide specific antigen (TPS) was negative and 90% in the two AD cases, respectively. PD-L1 TPS was not detected in the SCC cases.

### Surgery and outcomes

The surgical factors are displayed in Table 2. All eight patients received surgery and the median time from the end of neoadjuvant chemoimmunotherapy to surgery was 29 days (range, 25–32 days). No neoadjuvant chemoimmunotherapy-related surgical delays occurred. The median operation time was 242.5 min (range, 140–375 min). All of the patients underwent lobectomy, among which two underwent sleeve lobectomy and one received bronchoplasty. Five patients underwent open thoracotomy while the others underwent single-port video-assisted thoracoscopic surgery. Fibrosis of primary tumor and lymph nodes was observed in all of the patients (100%). Two patients suffered intraoperative bleeding requiring blood transfusion. Three patients suffered grade 2 surgical complications, including two cases of atrial fibrillation and one case of pulmonary air leakage. The median postoperative hospital stay was 7.5 days (range, 5–14 days). The surgical mortality rate at 30 days postoperatively was 0%.

### Radiographic findings and pathological response

The radiographic and pathological responses are recorded in Table 3. According to the radiographic findings, seven (87.5%) patients achieved a partial response, one had stable disease, and no one achieved a complete response or had progressive disease during the neoadjuvant treatment. The median sum of lesion diameter change from baseline was a 38.2% reduction (range, 30.0–63.6%) and the median of maximum standardized uptake value (SUVmax) change from baseline was a 52.75% reduction (range, 37.2–68.8%). The SUVmax change from the baseline of four patients was missing.

As for the pathological response, five (62.5%) cases achieved an MPR and no achieved a pathologic complete...
response (PCR). Among these patients, the primary tumor of one case reached PCR, but the left pulmonary ligament lymph node was positive, so we classified it as MPR. The other three patients who did not reach MPR also obtained a 10–20% tumor residue. The pathological assessment showed that R0 resection was achieved in all eight included patients (100%).

**Neoadjuvant TRAEs**

The TRAEs caused by neoadjuvant chemoimmunotherapy are shown in Table 4. Alopecia, anemia, and asthenia tied for the top three TRAEs of any grade, which occurred in seven of eight patients, followed by neutropenia (6/8) and nausea (6/8), pruritus (5/8), and rash (4/8). Neutropenia was the most frequent TRAE > grade 2 (3/8), followed by nausea (2/8). One grade 4 event was observed and no deaths occurred. No neoadjuvant treatment delays or drug dose reductions occurred because of TRAEs.

**Discussion**

Our results preliminarily showed that neoadjuvant chemoimmunotherapy with sintilimab plus chemotherapy was well tolerated and the TRAEs were acceptable. The high pathological response rate suggested that sintilimab with chemotherapy is promising and worthy of further study in neoadjuvant chemoimmunotherapy for stage III NSCLC.

Since long-term survival data requires a longer period of time to obtain and MPR is closely related to the prognosis of patients who receive neoadjuvant therapy, MPR is now considered an important method to evaluate the effect of
In this study, the MPR rate was 62.5%, which demonstrates the ideal effect of neoadjuvant sintilimab plus chemotherapy. This MPR rate is consistent with that reported by Sun et al. (62.5%) and is higher than that reported by Zhang et al. (43.3%) (14,15). The PCR rates reported by Sun et al. and Zhang et al. reached 31% and 20%, respectively, whereas none of the patients in our study reached PCR (14,15). This inconsistency can be explained by the different chemotherapy regimens and cycles. In our study, the proportion of patients who received one, two, and three cycles of treatment before surgery was 12.5%, 75%, and 12.5%, respectively, compared with 0%, 35%, and 65% in Sun et al. and 2%, 72%, and 20% in Zhang et al. (14,15). In addition, 6% of the patients in Zhang et al. received four cycles of treatment (14). More cycles seem to improve the efficacy of neoadjuvant chemoimmunotherapy.

In this study, we found that the sum of lesion diameter had an at least 30% reduction in the MPR group, which was consistent with previous studies (13,15). Regarding the relationship between PET-SUVmax and the postoperative pathological response, Zhao et al. found that the decline in the SUVmax was more extensive in the MPR/PCR groups compared to the non-MPR group (9). Similarly, all of the SUVmax values had a large reduction in the MPR group in our study. This suggested that the extent of SUVmax reduction might play a role in predicting the pathological response. Meanwhile, the cut-off value of SUV reduction between MPR and non-MPR requires further research (22). Tao et al. investigated the role of PET-CT in predicting MPR in lung cancer and found that all cases with a ΔSULpeak% <−30.0% (SUL: standardized uptake value corrected for lean body mass) achieved MPR. However, SUL is not commonly used in clinics (22).

We also evaluated the impact of sintilimab plus chemotherapy on surgery. We found that after neoadjuvant treatment, the primary lesions and lymph nodes had different degrees of fibrosis and adhesion with surrounding tissues, regardless of whether or not the patients achieved MPR. We considered that neoadjuvant sintilimab plus chemotherapy increases the difficulty of surgery. Thoracotomy, bronchoplasty, and sleeve resection are often needed, all of which will increase the risk of intraoperative bleeding and postoperative complications, including air leakage and arrhythmia. This is similar to the findings of Sun et al. and Zhang et al. (14,15). However, it is uncertain whether immunotherapy or chemotherapy is the main factor affecting the increased surgical difficulty. There is still no evidence suggesting that neoadjuvant chemoimmunotherapy increases the risk of surgical death (7,12,14,15).

In this study, the TRAEs of neoadjuvant sintilimab combined with chemotherapy were acceptable. The results showed that alopecia, nausea, asthenia, and neutropenia were the main TRAEs in our study and most of the TRAEs were grade 1–2. TRAEs > grade 2 were observed in 62.5% of patients, which is higher than that reported in previous studies. However, all of the patients with TRAEs > grade 2 recovered after short-term treatment. The most common TRAE > grade 2 in our research was neutropenia, which is similar to the findings of Sun et al., whereas Zhang et al. reported that hyperglycemia was the most common (14,15). Immune pneumonia is an important complication caused by immunotherapy (23); severe immune pneumonia will lead to death. Both Sun et al. and Zhang et al. reported the occurrence of severe pneumonia (14,15). However, no cases of severe pneumonia occurred in our study.

The limitations of our research are as follows: (I) this is a retrospective study; (II) the number of included cases is small, so it is impossible to perform further subgroup analysis, including by pathological type, gene mutation, PD-L1 score, and other factors, on the curative effect; (III) there was no control group; and (IV) the follow-up time was short. However, we believe that neoadjuvant sintilimab plus chemotherapy might be a promising therapeutic option for patients with locally advanced NSCLC.

Conclusions
Our results suggested that neoadjuvant sintilimab plus chemotherapy might be feasible for stage III NSCLC since it had a high MPR rate and acceptable TRAEs. However, long-term survival data and randomized controlled studies of neoadjuvant chemotherapy, chemoimmunotherapy, and immunotherapy are still needed.

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Footnote
Reporting Checklist: The authors have completed the STROBE and AME Case Series reporting checklists. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1194/rc
Data Sharing Statement: Available at https://tcr.amerigroups.com/article/view/10.21037/tcr-22-1194/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amerigroups.com/article/view/10.21037/tcr-22-1194/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This retrospective study was approved by the medical ethics committee of the Sixth Medical Center of Chinese PLA General Hospital (No. HZKY-PJ-2022-9), and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The informed consent for this retrospective research was waived.

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