Asynchrony of primary tumor and mediastinal lymph nodes response after neoadjuvant immunotherapy plus chemotherapy in a patient with stage IIIA non–small-cell lung cancer: a case report

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With the rapid development of immunotherapy, the efficacy and feasibility of neoadjuvant immunotherapy for early resectable non–small-cell lung cancer (NSCLC) has been demonstrated. However, there are still difficulties and controversies in evaluating the efficacy of neoadjuvant immunotherapy. In our report, we described a 43-year-old female patient who was diagnosed with stage IIIA (cT1N2M0) pulmonary adenocarcinoma. After two cycles of neoadjuvant immunotherapy (sintilimab) combined with chemotherapy, according to imaging evaluation, the efficacy of the primary lesion was evaluated as stable disease and the mediastinal lymph nodes were evaluated as partial response. However, the postoperative pathological evaluation showed the primary lesion was pathological complete response and the mediastinal lymph nodes were major pathological response. This indicated that neoadjuvant chemo-immunotherapy was effective for both primary and mediastinal lymph nodes, but regression of the lesions was not synchronous. This study provided a complete process of neoadjuvant treatment, illustrating the effectiveness and safety of neoadjuvant chemo-immunotherapy to a certain extent. It is also suggested that the evaluation of neoadjuvant immunotherapy should be combined with imaging and pathology, and the primary tumor and lymph nodes should be evaluated, respectively.

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Introduction

Lung cancer is one of the highest morbidity and mortality among all cancers worldwide, with around 80–85% of them are non–small-cell lung cancer (NSCLC) and almost 20% of NSCLC patients are diagnosed with stage IIIA (N2) [1,2]. Although these patients have potentially resectable tumors, the prognosis is still poor, and most of them will experience disease progression after surgery. During recent decades, neoadjuvant chemotherapy has achieved encouraging outcomes, which help downgrade tumors and make inoperable tumors operable. Compared to operation alone, the 5-year overall survival (OS) rate of preoperative standard platinum-containing doubles combined with surgery increased from 40 to 45%, of which stage IIIA improved from 20 to 25%. However, approximately 43% of patients still had different degrees of local or/and distant recurrence [3]. The above survival data are still unsatisfying. Besides, the toxic and side effects of standard chemotherapy are relatively large, more than 60% of patients will undergo grades 3–4 toxicity. Therefore, it is still necessary for us to explore new neoadjuvant therapy, which could improve long-term survival and reduce the adverse effects (AEs).

Immune checkpoint inhibitors (ICIs) can enhance the antitumor immune response, which mainly act by inhibiting programmed cell death-1/programmed cell death-ligand 1 (PD-1/PD-L1) receptor or the cytotoxic T lymphocyte-associated protein-4 (CTLA-4) receptor [4]. To date, the treatment of ICIs has made significant progress in advanced lung cancer, but there is still lack of conclusive evidence for early lung cancer. More and more people around the world are gradually focusing on immunotherapy in early-stage lung cancer, and corresponding clinical studies have also been initiated. According to some clinical trials, neoadjuvant immunotherapy combined with chemotherapy can bring more survival benefits to NSCLC patients, and the AEs can be tolerable [5]. Sintilimab, a highly selective recombinant humanized mAb that blocks the interaction of PD-1 and its ligands, has been verified to enhance antitumor response [6]. It

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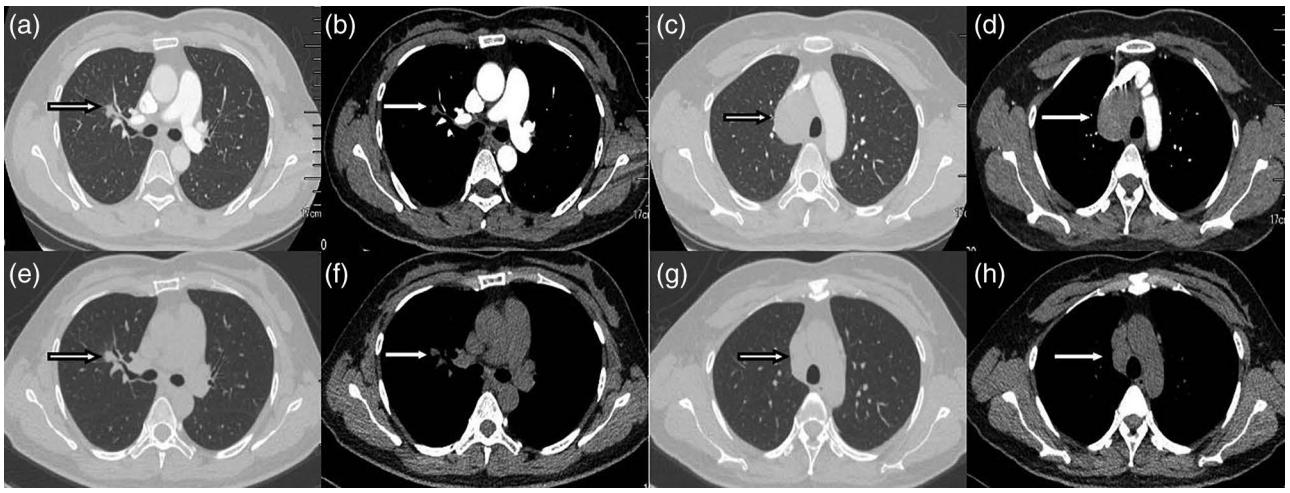
was approved to treat classical Hodgkin lymphoma by the National Medical Products Administration of China in 2020 [7]. However, there are few studies on sintilimab in neoadjuvant therapy for lung cancer, and the evidence of efficacy is insufficient. Herein, we presented a patient of stage IIIA NSCLC with negative mutation. After two cycles of neoadjuvant sintilimab plus chemotherapy, it was found that the asynchrony of primary tumor and mediastinal lymph nodes remission, and the mismatch between the imaging and pathology. This case indicated that the combination of sintilimab and chemotherapy is likely to be considered as optional management for resectable NSCLC. As of this writing, the patient's vital signs were stable and no signs of recurrence were observed.

Case report

A 43-year-old woman came to the hospital due to an occupation of the upper lobe of the right lung during physical examination. The chest computed tomography (CT) revealed a nodule in the upper lobe of the right lung (0.8×0.4 cm), with bulky swollen mediastinal lymph nodes (4.4×3.3 cm) on 22 October 2020 (Fig. 1a–d). The patient had no systemic symptoms such as chest pain, hemoptysis, or significant weight loss. She also denied a history of smoking and other pulmonary diseases. After admission, further improvement of positron-emission tomography/CT (PET/CT) indicated that the right upper lobe nodule had mild fluorodeoxyglucose-avid, and malignant lesions were not excluded (Fig. 2a). At the same time, there were high metabolic nodules and masses in the mediastinum 2R and 4R groups (Fig. 2b and c). Considering the increased metabolic rate of the mass, the possibility of malignant lesions was high. Tumor marker tested on 23 October 2020 showed: CEA145.20 ng/mL, CA199 27.47 ng/mL, and CA724 7.17 ng/mL. In order to further clarify the pathological nature of the patient, she underwent a needle biopsy of mediastinal lymph nodes. The pathological results reported lung adenocarcinoma, and the immunohistochemistry revealed that Ki-67 was over 60% (Fig. 3a). The percentage of PD-L1 immunostaining showed high expression with more than 50%. Moreover, the gene mutation was negative (EGFR/ALK/KRAS/RET/ROS1) and there was no evidence of distant metastatic disease. Therefore, the clinical staging for this patient was cT1N2M0 (stage IIIA) according to the eighth edition lung cancer stage classification [8].

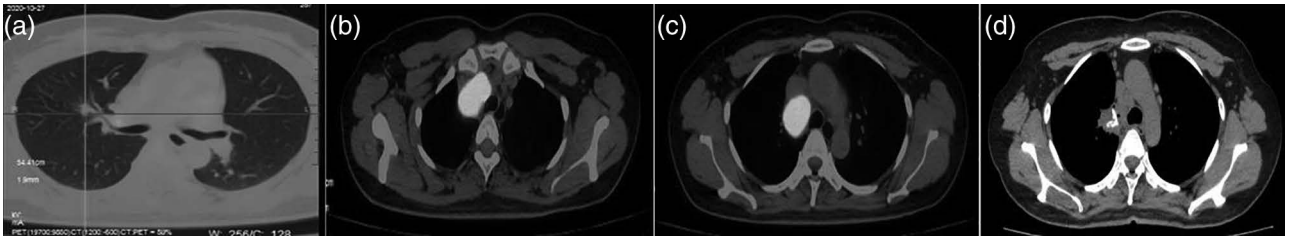
When performing the evaluation by the multidisciplinary treatment in our hospital, considering that the mediastinal lymph nodes were swollen and might invade the superior vena cava and azygos vein, which may increase the risk and difficulty of operation. In order to complete the removal by surgery and preserve the residual lung function as much as possible, it was practicable for the patient to perform immunotherapy plus chemotherapy as neoadjuvant therapy. Therefore, she received two cycles (3 weeks for one cycle) of sintilimab combined with nab-paclitaxel and carboplatin prior to surgery in November 2020. During the neoadjuvant treatment, the patient had no obvious AEs and no grade 4 toxicities were recorded. After the first two cycles of the treatment, the target lesion was slightly reduced (0.8×0.3 cm) and the efficacy was evaluated as stable disease (Fig. 1e and f). Meanwhile, the mediastinal lymph nodes were significantly narrower compared to before (2.2×1.7 cm) and the efficacy was evaluated as partial response (PR) on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Fig. 1g and h) [9]. Ultimately, the patient underwent the surgery of right upper lung lobectomy plus lymph

Fig. 1



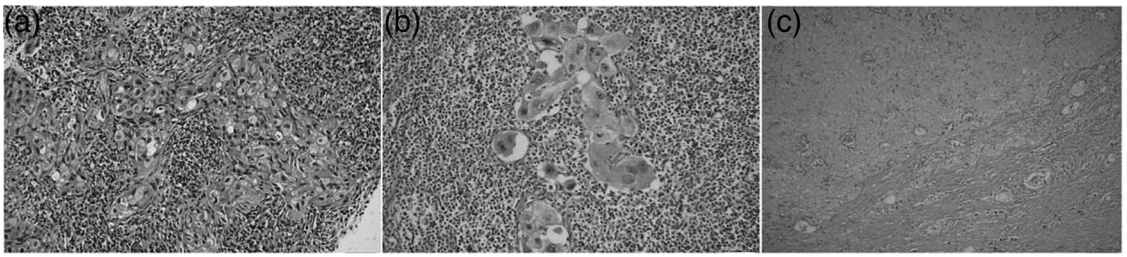
Evaluation of imaging efficacy. Chest CT scan showing the clinical response to neoadjuvant chemo-immunotherapy. (a–d) Chest CT images before neoadjuvant therapy on 22 October 2020. (e–h) Chest CT images after two cycles of neoadjuvant therapy on 1 December 2020. CT, computed tomography.

Fig. 2



PET-CT and chest CT images before and after the follow-up treatment. (a) PET-CT image before neoadjuvant therapy. Mildly FDG-avid mass in the upper lobe of the right lung (SUV_{max} =1.0). (b, c) PET-CT images before neoadjuvant therapy. Intensely FDG-avid lymph nodes in the mediastinum 2R and 4R groups (SUV_{max} =14.0). (d) Chest CT image after surgery, lung CT showed no recurrence of tumor. CT, computed tomography; FDG, fluorodeoxyglucose; SUV_{max}, maximum of standard uptake value.

Fig. 3



Pathological images. (a) Hematoxylin and eosin (HE) stains of the lymph nodes with viable tumor cells before neoadjuvant therapy. (b) HE stains of the lymph nodes with highly degenerative tumor cells after neoadjuvant therapy. (c) HE stains of the primary tumor bed with no surviving tumor cells after neoadjuvant therapy.

nodes dissection via thoracoscopy on 15 December 2020 and achieved the goal of margin-negative (R0) resection. To our surprise, postoperative chronic pathology revealed that no cancer residue in the primary tumor of the right lung instead showed mainly fibrosis, scattered chronic inflammatory cell infiltration, and was evaluated as pathological complete response (pCR) (Fig. 3c). However, only a few metastatic tumor cells remained in the mediastinal lymph nodes. These tumor cells were highly degenerative with increased cell size, ill-defined cytoplasm, and eosinophilic cytoplasm, within which vacuoles and nuclear debris were evaluated as major pathological response (MPR) (Fig. 3b). The tumor marker tested on 15 December 2020 showed: CEA 7.00 ng/mL, CA199 1.21 ng/mL, CA724 4.26 ng/mL. The patient was discharged on the third day after the operation without perioperative complications. One month after the operation, the patient's lung CT showed good postoperative healing with no abnormality (Fig. 2d), and then the patient received two cycles of adjuvant chemo-immunotherapy from January to February 2021. At present, the patient remained undergoing regular tumor follow-up to carefully monitor the possible recurrence of the disease.

Discussion

In recent years, ICIs have made breakthroughs and progress in the treatment of advanced NSCLC. Several clinical trials have manifested that neoadjuvant therapy with anti-PD-1 immunotherapy could produce good long-term effects in patients with resectable I-IIIA NSCLC [10]. The NADIM study, a phase II trial involving 46 patients with stage IIIA (N2) NSCLC, added nivolumab to neoadjuvant chemotherapy for three cycles (q3w) prior to surgery resection and followed by adjuvant nivolumab monotherapy for one year. The result demonstrated that after three cycles of neoadjuvant chemotherapy, 4% (2/46) achieved CR, 72% (33/46) reached PR, 24% (11/46) had stable disease according to RECIST 1.1 criteria, and no patients had progressive disease (PD) during immunotherapy. Among them, 41 patients underwent subsequent surgery, with 34 (83%) patients showing MPR and 26 (63%) showing pCR [11]. These results encourage that preoperative chemotherapy plus PD-1 inhibitor is profitable for patients with resectable NSCLC.

According to recent research, sintilimab plus chemotherapy had a good effect as a first-line treatment for nonsquamous NSCLC. In this study, the sintilimab-combination group was found to prolong the progression-free survival (8.9 m vs. 5.0 m, 95% CI, 36.2–64.3%) and objective response rate (51.9% vs. 29.8%) when compared with the placebo-chemotherapy group [12]. Regarding the efficacy of sintilimab in neoadjuvant therapy, another phase 1b study (ChiCTR-OIC-17013726) based on a total of

40 NSCLC patients (stages IA–IIIB) with negative gene mutation, including 33 cases (82.5%) of squamous carcinoma and seven cases of adenocarcinoma (17.5%). All patients received two cycles of sintilimab treatment (200 mg, q3w) and then 37 patients received radical resection. The results showed that 15 of 37 patients (40.5%, 95% CI, 30.2–66.9%) achieved MPR, of which 6 of 37 patients (16.2%, 95% CI, 6.2–32.0%) reached pCR. In particular, this study also found that pathologic regression and MPR were observed regardless of the expression of PD-L1 [13]. In terms of safety, the latest report showed that the addition of sintilimab did not seem to increase the incidence of common AEs in platinum-based chemotherapy [6]. However, more clinical studies are required to explore the role of sintilimab in the neoadjuvant chemo-immunotherapy of NSCLC.

On the basis of the above research, our case is a successful report of chemo-immunotherapy as neoadjuvant therapy. We speculate that the reasons for the successful treatment may be related to the following points. To begin with, the tumor burden is relatively large before tumor resection, and the exposure of antigen will greatly enhance the degree and duration of tumor-specific T cell response, trigger a long-lasting anti-tumor effect, and then allow the immune system to better kill the tumor [14]. Moreover, the application of PD-1 blockers before surgery can also continuously generate more memory-specific CD8+ T cells in the peripheral blood to realize long-term tumor monitoring and prevent tumor recurrence [15]. For our patient, she had a high tumor burden and high Ki-67 level (>60%) that reflected the malignant degree of tumor cells [16]. In addition, the patient's immunotherapy predictor PD-L1 expression level was slightly higher (>50%). As a consequence, these may be the reason for the success of chemo-immunotherapy for the patient as neoadjuvant therapy in the above situation.

At present, there are no standard guidelines regarding the evaluation of efficacy after neoadjuvant therapy for lung cancer in clinical practice. Traditionally, the primary outcome of adjuvant therapy needs to be assessed by disease-free survival (DFS) and OS for long-term follow-up [17]. Nevertheless, the survival benefit of neoadjuvant therapy can be more efficiently assessed by pathologic remission, which includes MPR and pCR [18]. Recent studies have shown that pathological staging has a significant effect on survival rate, and MPR is positively correlated with OS [19]. In our report, the pathological reaction rate of mediastinal lymph nodes (MPR) was lower than that of primary lesion (pCR). The main reason for the asynchrony between them may be related to the special structure of lymph nodes or the particularity of peripheral blood circulation. In addition, it may also represent that due to biological heterogeneity, the occult regional or systemic metastases have poor response to chemotherapy [20]. Moreover, the postoperative DFS time of the patient was more than 3 months, which proved the effectiveness of immunotherapy combined with chemotherapy, and further predicted a good prognosis. Although there was no sign of recurrence, it still merited further follow-up to gather better outcomes.

The peculiarity of our case report was that adding sintilimab to neoadjuvant treatment could downstage the patient's tumor and finally achieved R0 resection. Considering the patient's younger age, complete tumor resection was of realistic significance to maintain the quality of life in the future. In particular, the imaging findings after adjuvant chemo-immunotherapy may not be consistent with the postoperative pathology. Although some residual primary lesions and mediastinal lymph nodes could still be seen in the imaging, the postoperative pathology revealed mostly relieved. Considering that it may not be the reason for tumor, but rather possibly related to the stimulation of lymphocyte proliferation by PD-1 mAb. Therefore, when evaluating the efficacy of neoadjuvant immunotherapy, it may not only be assessed from the perspective of imaging, the final evaluation needs to be combined with pathology to be more objective. However, this is just one patient, the guiding role of evaluation methods in neoadjuvant therapy needs to be further investigated.

In summary, the addition of sintilimab to neoadjuvant chemotherapy may be a promising therapeutic choice for patients with IIIA NSCLC. This case provides a potentially satisfactory neoadjuvant regimen for NSCLC in clinical practice, whereas subsequent follow-up is still needed to fully support the treatment strategy's rationality.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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