Case Report

Pathological complete response to radical surgery after receiving durvalumab plus neoadjuvant chemotherapy for 1 limited-stage small cell lung cancer patient: a case report

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Background: Small cell lung cancer (SCLC) is clinically the most aggressive subtype of lung cancer, and accounts for about 15% of all newly diagnosed lung cancer cases. Approximately 1/3 of SCLC patients are diagnosed with limited-stage SCLC (LS-SCLC). The standard of treatment for most patients with LS-SCLC is concurrent chemoradiotherapy. LS-SCLC is sensitive to first-line therapy, but has a high recurrence rate and patients show a poor response to second-line treatment. Referring to extensive-stage SCLC (ES-SCLC), durvalumab plus platinum-etoposide chemotherapy has been approved by the Food Drug Administration and National Medical Products Administration. It is hoped that durvalumab will produce good results for LS-SCLC patients.

Case Description: In this article, we report the case of a 75-year-old male patient with LS-SCLC of the left lung (tumor, node metastasis stage cT3N0M0 IIB) who received 2 cycles durvalumab plus neoadjuvant chemotherapy. The neoadjuvant therapy was favorable and no adverse events were observed. The assessment of the tumor via Resist1.1 by videography indicated a complete response. Then a thoracoscopic resection of the left lower lobe of the lung was performed under general anesthesia. The operation was successful, and the patient's postoperative recovery was good. Fortunately, the postoperative pathology results showed pathological complete response. After the surgery, the patient received 3 cycles of adjuvant therapy. Now, the patient is still alive and there is no sign of tumor recurrence.

Conclusions: This case highlights the benefits of neoadjuvant programmed death-ligand 1 (PD-L1) inhibitor plus chemotherapy and radical surgery for patients with LS-SCLC and identifies a significant treatment option for LS-SCLC patients.

Keywords: Limited-stage small cell lung cancer (LS-SCLC); case report; durvalumab; neoadjuvant chemotherapy; pathological complete response

Submitted Feb 11, 2022. Accepted for publication Apr 13, 2022.
doi: 10.21037/tcr-22-729
View this article at: https://dx.doi.org/10.21037/tcr-22-729

Introduction

In recent years, lung cancer has become the most common cancer around the world (1). It is also the leading cause of cancer-related deaths worldwide, and accounts for 18.4% of all cancer-related deaths (1). Small cell lung cancer (SCLC) accounts for about 15% of lung cancer cases. It is characterized by rapid growth and extensive early metastasis (1). Under the classification of The Veterans' Administration Lung Study Group, SCLC include limited-stage SCLC (LS-SCLC) and extensive-stage SCLC (ES-SCLC) (2). LS-SCLC refers to cases that are confined to the ipsilateral hemithorax and local lymph nodes, and can be safely surrounded by a single radiation field. The cases that initially cannot receive radiotherapy are classified as ES-SCLC (3).

Surgery plus adjuvant chemotherapy is the standard

treatment for patients with limited T1–2N0 SCLC. Studies have shown that patients with lymph node negative SCLC treated with surgery plus adjuvant chemotherapy could receive longer survival compared with surgery alone or concurrent chemoradiotherapy (4,5). Etoposide + cisplatin (6) or etoposide + carboplatin (7) are the first choice for adjuvant chemotherapy. However, for LS-SCLC beyond T1–2N0M0, additional chest radiotherapy is better than chemotherapy alone (8), and concurrent chemoradiotherapy is better than sequential chemoradiotherapy (9). Currently, the optimal dose and scheme of chest radiotherapy are unknown. The majority of patients respond to initial therapy, but then they will experience disease relapse. The overall survival (OS) rate of LS-SCLC patients is only 30–35% (10).

Durvalumab is a programmed death-ligand 1 (PD-L1) blocking antibody that enables T cells to recognize and kill tumor cells (11). In the CASPIAN study, the first-line treatment of durvalumab plus platinum-etoposide significantly improved the OS of patients with ES-SCLC (12). However, for LS-SCLC, there have been no breakthroughs in immunotherapy. The ADRIATIC trial (ClinicalTrials.gov identifier, NCT03703297), an ongoing global randomized clinical trial (RCT), investigates the efficacy and safety of durvalumab with or without tremelimumab for patients with LS-SCLC after finishing concurrent chemoradiotherapy. We sincerely hope that the data of ADRIATIC trial will change the treatment landscape of LS-SCLC. In LS-SCLC, surgical treatment is only applicable to T1–2N0 patients. Radiotherapy and chemotherapy are still of great significance in the treatment of patients with LS-SCLC. The initial response rate is high, but relapsed and refractory patients are still difficult to treat. Many clinical trials have examined the use of immune checkpoint inhibitors plus neoadjuvant chemotherapy in treating resectable NSCLC, and found that this treatment achieves good clinical outcomes (13,14). Thus, we hypothesized that durvalumab plus neoadjuvant chemotherapy would also be a good treatment option for LS-SCLC.

In this article, we report for the first time a case of LS-SCLC who showed a pathological complete response after receiving durvalumab plus neoadjuvant chemotherapy and radical surgery. It's a very valuable case and we hope this case can provide some treatment experience for LS-SCLC in the future. We present the following article in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-729/rc).

Case presentation

On April 21, 2020, a 75-year-old male was hospitalized mainly for cough, expectoration, and bloody sputum. The patient had smoked about 25 cigarettes per day for 40 years, but had quit smoking 20 days ago. He had also drunk alcohol for 20 years, 150 ml each time, but had stopped drinking 3 years ago. No other special personal or family history was reported. The patient had a performance-status score of 2 points. The tumor markers showed that the pro-gastrin-releasing peptide (ProGRP) level was 677.50 pg/mL and the neuron-specific enolase (NSE) level was 21.61 ng/mL, both of which were higher than normal values. The bronchoscopy showed local uplift and hyperplasia of bronchial mucosa in the basal segment of the lower lobe of left lung. The pathology and immunohistochemistry of the bite examination suggested small cell carcinoma. Computed tomography (CT) imaging showed masses in the left lower hilum and left lower lobe of the lung, micronodules in the left lower lobe, interstitial changes in the lower lobe of both lungs, emphysema, a small cyst in the left lobe of the liver, and multiple cysts in both kidneys (see *Figure 1*). Skull CT and bone imaging showed no abnormalities. The patient was diagnosed with LS small cell carcinoma of the left lung (tumor, node metastasis stage cT3N0M0 IIB).

According to the Chinese Society of Clinical Oncology guidelines, the role of surgery in stage IIB–IIIA SCLC is still controversial, and concurrent chemoradiotherapy is recommended. Based on the findings of the CASPIAN study, we decided to administer durvalumab plus neoadjuvant chemotherapy. On April 22, 2020 and May 19, 2020, the patient received etoposide (0.5 g) plus lobaplatin (50 mg) and durvalumab (500 mg) for 2 cycles. The process was favorable and no adverse events were observed. After 2 cycles, the ProGRP and NSE levels decreased to 62.23 pg/mL and 12.28 ng/mL, respectively, and both returned to the normal values. The CT re-examination showed post-chemotherapy changes in the left lower lobe, a slightly larger pulmonary hilum than normal, and a smaller range than before (see *Figure 2*). At baseline, the diameter of the tumor in the left lower hilum of the lung was 4.3 cm, and the diameter of the tumor in the left lower lobe was 3.6 cm. After two cycles of neoadjuvant therapy, we can see no clear mass on the CT of the lung (see *Figure 2*). The assessment of the tumor via Resist1.1 by videography indicated a complete response (15). On June 28, 2020, a thoracoscopic resection of the left lower

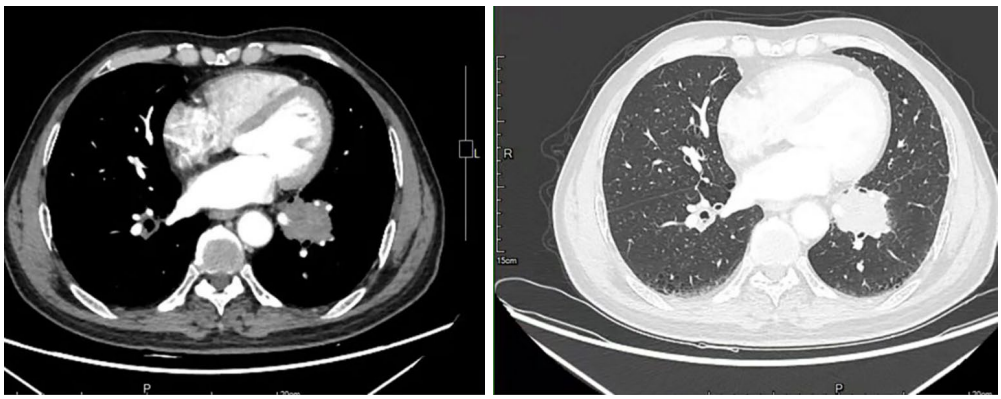

Figure 1 CT of baseline. CT, computed tomography.

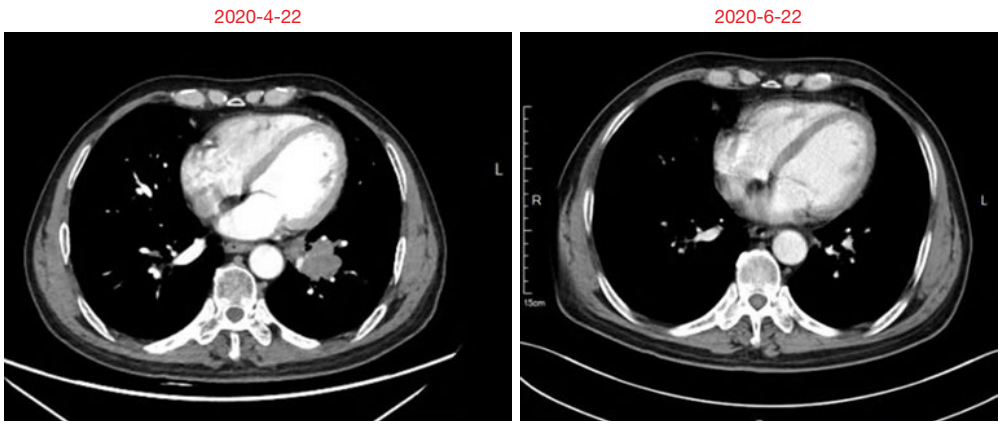

Figure 2 Comparison between before and after treatment.

lobe of the lung was performed under general anesthesia. The operation was successful. The patient's postoperative recovery was good, and the patient was discharged smoothly.

The postoperative pathology results showed that the lung tissue was 15 cm × 11 cm × 4 cm and the bronchial mucosa was smooth, and no obvious tumor was observed in the multi section incision (see *Figure 3A*). The lung tissue of the tumor bed showed chronic inflammation and carbon dust deposition, and no residual cancer was found. The results were as follows: bronchial stump (–); lymph nodes: 0/1 in group 5, 0/2 in group 7, 0/2 in group 9, 0/3 in group 10, and 0/11 in group 11; and stage: ypT0N0M0. A chest X-ray examination was performed after surgery (see *Figure 3B*). Postoperative changes in the cancer in the left lung were observed. After the surgery, the patient received etoposide (0.5 g) plus lobaplatin (50 mg) and durvalumab (500 mg) for 3 cycles. Subsequently, the patient received regular reexamination and follow-up. Now, the patient is still alive and there is no sign of tumor recurrence. The timeline of the case is shown in *Figure 4*.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Here, we reported a case of a 75-year-old male patient with LS-SCLC of the left lung (tumor, node metastasis stage cT3N0M0 IIB) who received 2 cycles durvalumab plus neoadjuvant chemotherapy. The neoadjuvant therapy was favorable and no adverse events were observed. Then

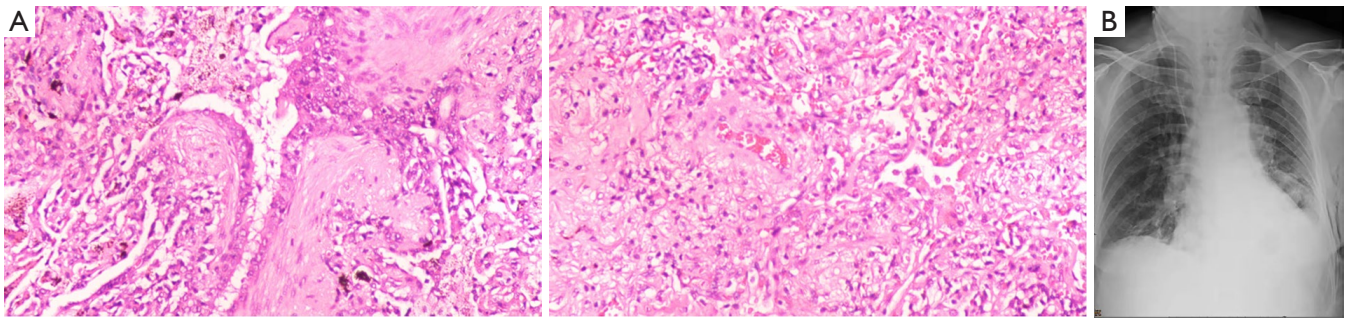

Figure 3 Postoperative pathology and chest X-ray. (A) Pathology. (B) Chest X-ray. (A) The lung tissue at the tumor bed showed chronic inflammation and charcoal deposition. No residual carcinoma was observed. (Hematoxylin-eosin staining, 200 times magnification). (B) Chest X-ray after surgery.

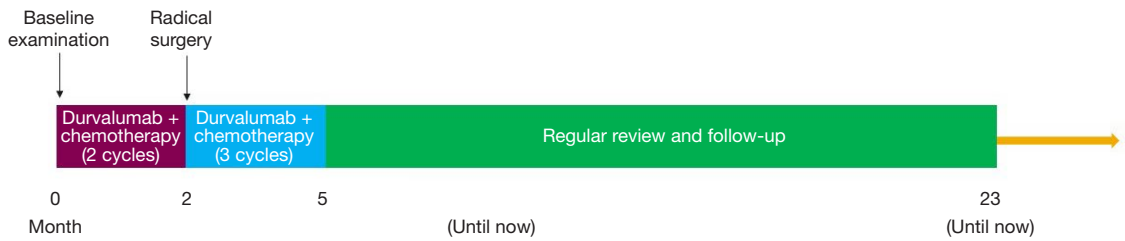

Figure 4 The timeline of the case.

a thoracoscopic resection of the left lower lobe of the lung was performed under general anesthesia. The operation was successful, and the patient's postoperative recovery was good. Fortunately, The postoperative pathology results showed pathological complete response. After the surgery, the patient received 3 cycles of adjuvant therapy. Now, the patient is still alive and there is no sign of tumor recurrence.

Cytotoxic T cells are key for the immune system to kill tumors, and the PD-L1/programmed cell death protein 1 (PD-1) pathway is the main pathway for immune escape. PD-1/PD-L1 inhibits T cell function through multiple signaling pathways, enabling PD-(L)1 inhibitors to play an anti-tumor role by promoting immune normalization (14). Durvalumab is an anti-programmed cell death receptor-1 antibody that blocks the PD-L1 from binding to the PD-1 and CD80, thus helping to restore the endogenous anti-tumor T cell response.

In the CASPIAN study, the researchers evaluated the efficacy of durvalumab combined with or without tremelimumab + etoposide plus cisplatin or carboplatin in patients who had been newly diagnosed with ES-SCLC. In total, 268 patients were randomly assigned to the durvalumab combined with platinum + etoposide group, and 269 patients were randomly assigned to the platinum + etoposide group. Durvalumab combined with platinum + etoposide significantly improved patients' OS (12). These findings suggested that the combination of durvalumab and platinum + etoposide significantly improved the OS of patients with ES-SCLC. Based on the results of this study, durvalumab in combination with etoposide and either carboplatin or cisplatin as a first-line treatment of ES-SCLC has been approved by Food and Drug Administration (16). Currently, there is very little evidence about the effect of immune checkpoint inhibitors on LS-SCLC.

For patients with stage I–IIA LS-SCLC, research has shown that the 5-year survival rates of the surgical group and the non-surgical group are 27–73% and 4–44%, respectively, which suggests that patients can benefit from surgery (17). In a propensity-matching analysis based on the National Cancer Database, Yang *et al.* (4) found that surgical treatment compared with concurrent chemoradiation significantly improved the 5-year survival rate of patients (47.6% *vs.* 29.8%; P<0.01). In terms of surgical methods, a number of retrospective studies and meta-analyses (4,18) have shown that the survival of the lobectomy group was better than that of the wedge-resection group.

However, for patients with stage IIB–IIIA LS-SCLC, the role of surgery is still controversial (17). Some retrospective studies (17) have found positive results, but the median survival time obtained in these studies (17) ranges from 17–31.7 months, which does not represent a breakthrough compared to the 25 months in the CONVERT study (19) with concurrent chemoradiotherapy. Thus, the effectiveness and suitability of surgery for stage IIB–IIIA SCLC remains unclear.

Radical surgery is only recommended for LS-SCLC patients with T1–2N0M0 cancer staging, and <5% of patients with SCLC meet this criteria at the time of their initial diagnosis of SCLC (20). Most LS-SCLC patients are beyond T1–2N0, and should receive concurrent chemoradiotherapy. In the first-line treatment, the effective rate is about 80%, but the majority of patients will relapse in 6 months after finishing the initial treatment (21). Here is a study to compare the efficacy of surgery with concurrent chemoradiotherapy in the patients diagnosed with LS-SCLC (22), 102 patients received concurrent chemoradiotherapy were involved into the CCRT group (the patients who received concurrent chemoradiotherapy), and the CCRT group was selected as control group. Referring to the order of adjuvant therapy, S group contain SA group and NS group. There are 30 patients in SA group, and these patients received adjuvant chemotherapy and radiotherapy. Different from SA group, there were 20 cases in NS group, and the patients received neoadjuvant chemotherapy. The results indicated that both the median progression-free survival (PFS) and the median OS of the S group were notably longer than the CCRT group (P<0.0001). In subgroup survival analysis, we can saw that there were no significant difference between NS group and SA group. This study indicated that, for LS-SCLC patients, radical surgery combined with perioperative chemotherapy and adjuvant radiotherapy may be a better choice.

It is clear that preoperative neoadjuvant chemotherapy has better survival benefits than surgery alone or concurrent chemoradiotherapy alone, but there is still a long way to go to optimize the benefit of long-term survival. Several previous studies have shown that immunotherapy has great potential in the neoadjuvant therapy of NSCLC, and research has shown that 20–85% of patients achieve major pathological remission, which is better than the findings of previous neoadjuvant chemotherapy studies (23,24). However, research on immunotherapy in neoadjuvant therapy in LS-SCLC are limited. The use of targeted drugs in the treatment of NSCLC has been shown to significantly improve the clinical prognosis and quality of life of patients (25). However, for LS-SCLC, the use of targeted drugs is still in the research stage, and there are no clinical trial findings confirming their efficacy (26).

In this case, we tried a new method in the treatment of LS-SCLC, and found that durvalumab plus neoadjuvant chemotherapy had promising anti-tumor efficacy. The strengths of the treatment are the patient received pathological complete response and there were no adverse event. Furthermore, there are still some limitations of this case. Firstly, further research needs to be conducted to determine whether the pathological complete response can turn into long-term survival. Secondly, the post-surgery treatment of this patient still needs to be explored. Thirdly, we should conduct a randomized control trial of large samples to verify the efficacy and safety of this treatment. Inconclusion, this case provides a new treatment option for patients with LS-SCLC, and we can see the effect of immunotherapy plus neoadjuvant chemotherapy in treating SCLC, which should be further explored in the future. Further, more clinical trials are needed to provide stronger evidence to guide the clinical practice of LS-SCLC.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-729/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-729/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. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is

available for review by the editorial office of this journal.

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(English Language Editor: L. Huleatt)

Cite this article as: Li Z, Zhang B, Yang F, Yang L. Pathological complete response to radical surgery after receiving durvalumab plus neoadjuvant chemotherapy for 1 limited-stage small cell lung cancer patient: a case report. Transl Cancer Res 2022;11(4):973-979. doi: 10.21037/tcr-22-729

