Case Report

Immuno-based therapeutic strategies for initial unresectable locally advanced non-small cell lung cancer: a case report

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Abstract: Lung cancer is the leading global cause of cancer-related deaths. Even for patients who receive multidimensional treatment, the prognosis for locally advanced lung cancer is poor. The outcomes of neoadjuvant immunotherapy have been encouraging in many types of cancer, and especially lung cancer. However, the prognoses of patients with initially unresectable non-small cell lung cancer (NSCLC) with T4 or bulky swollen N2 lymph nodes are still unsatisfying, and novel therapeutic modalities are desperately needed. Here, we present a case of a patient with initially unresectable NSCLC with T4 and bulky swollen N2 lymph nodes, and present the argument for neoadjuvant immuno-based therapeutic strategies as a reasonable option for such patients.

Keywords: Neoadjuvant therapy; immunotherapy; lung cancer

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Introduction

Globally, lung cancer is responsible for more deaths than any other cancer. The clinical management of locally advanced disease, which accounts for about 30% of non-small cell lung cancer (NSCLC) cases, is highly challenging because of the poor prognosis, even in the wake of multidimensional treatment modalities (1).

In recent years, therapeutic strategies for patients with NSCLC and many other tumor types have been changed enormously by immunotherapy based on immune checkpoint inhibitors. Despite the encouraging outcomes of neoadjuvant immunotherapy seen in recent trials, such as the NEOMUN and NADIM trials, the prognoses of patients with initially unresectable NSCLC with T4 or bulky swollen N2 lymph nodes are still unsatisfying (2,3). For this reason, novel therapeutic modalities are desperately needed. Here, we present our experience of an immuno-based therapeutic strategy for a patient with initially unresectable NSCLC with T4 and bulky swollen N2 lymph nodes. We present the following case in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/tlcr-20-517).

Case presentation

A 56-year-old male with no history of smoking was admitted to the hospital complaining of non-productive cough on March 29, 2019 (*Figure 1*). A chest CT scan revealed a heterogeneous, infiltrative, 7.7 cm × 6.2 cm mass in the patient's right upper lung with bulky swollen mediastinal and hilar lymph nodes (*Figure 2*). Percutaneous CT-guided needle biopsy revealed adenocarcinoma from the mass. ^{18}F-FDG positron emission tomography (PET) indicated positive mediastinal and hilar lymph nodes (stations 2, 4, 7, and 10). Molecular testing illustrated pan-negative results for commonly known oncogenic driver mutations. Ventana ALK (D5F3, Ventana Medical Systems Inc., Oro Valley, AZ, USA) immunohistochemistry (IHC) also demonstrated a negative result. IHC test of

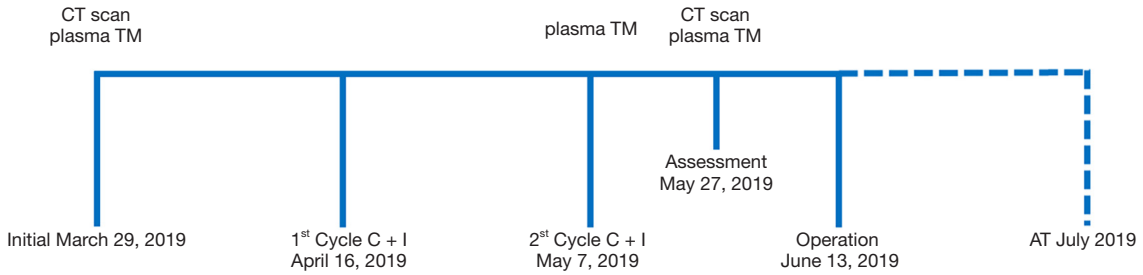


Figure 1 Schematics showing the timeline of treatment. A solid line indicates treatment conducted, while a dashed line indicates consequent plans. CT, computed tomography; TM, tumor markers; C+I, chemo-immunotherapy; AT, adjuvant treatment.

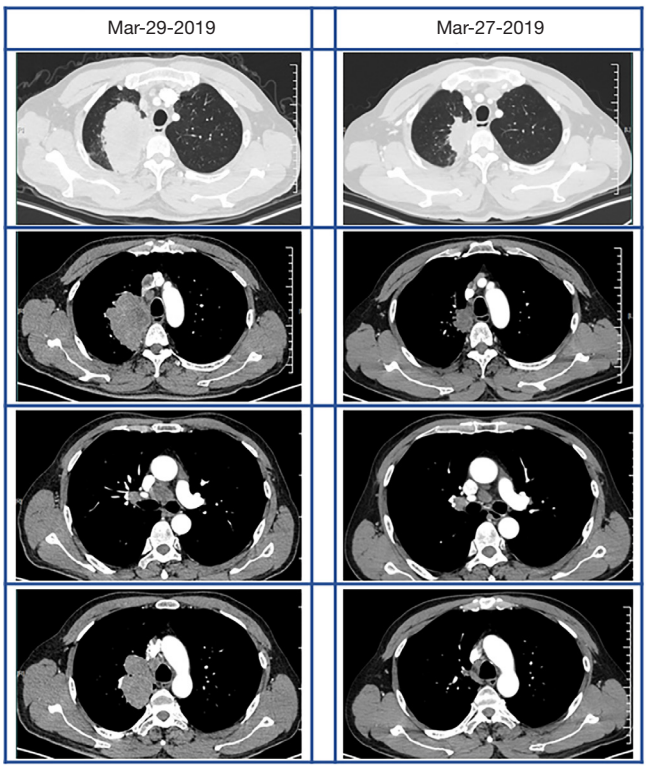


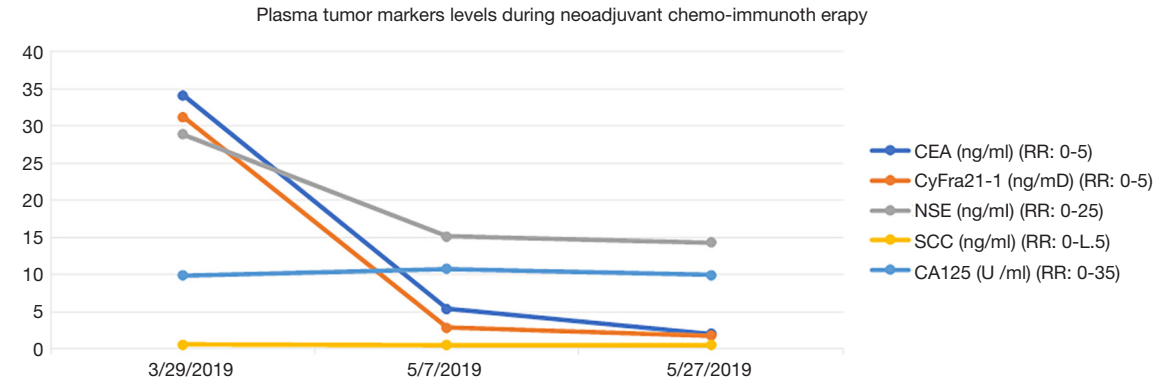
Figure 2 Computed tomography scans showing the clinical response to neoadjuvant chemo-immunotherapy. Computed tomography scans of the lung window and mediastinal window before and after two cycles of neoadjuvant chemo-immunotherapy illustrate significant shrinkage of the lung mass together with mediastinal and hilar lymph nodes.

CST-PD-L1 (E1L3N®) detected a PD-L1-positive rate of 10% in the NSCLC tumor cells. Consequently, the patient was diagnosed with stage IIIB (T4N2M0) lung adenocarcinoma. After discussing the patient's case, the lung cancer multi-disciplinary team (MDT) decided on a treatment of pemetrexed and carboplatin, in combination with pembrolizumab 200 mg every 3 weeks. After 2 cycles of chemo-immunotherapy, a repeat chest CT scan revealed that the right upper lung mass had reduced in size to 4.6 cm, with shrinking mediastinal and hilar lymph nodes (*Figure 2*). A steady decrease in the levels of plasma tumor marker, such as CEA, CyFra21-1, and NSE, was also observed (*Figure 3*).

Another lung cancer MDT discussion after the second cycle of chemo-immunotherapy concluded that the patient would undergo surgical treatment. Four weeks after the completion of the neoadjuvant chemo-immunotherapy course, a right upper lobectomy with mediastinal lymphadenectomy was performed. The final pathology report revealed a 5.5-cm, T3N2 adenocarcinoma. The patient's postoperative courses include subsequent adjuvant immunotherapy for a one-year period, as the adjuvant treatment in the NADIM trial, and radiotherapy.

Discussion

Locally advanced NSCLC represents a heterogeneous group of tumors, varying from resectable types with microscopic lymph nodes metastases to unresectable tumors with multiple bulky swollen N2 lymph nodes. During recent decades, the benefit of neoadjuvant chemotherapy for the survival rate of such patients has been put forward (4). The majority patients with locally advanced NSCLC whose disease is initially unresectable experience disease progression, despite definitive concurrent chemoradiotherapy (5). For the patient in our case report, despite being defined as initially unresectable, he was judged as a potentially resectablecase following the MDT discussion, based on Chinese guidelines for diagnosis and treatment of primary lung cancer (6). Therefore, neoadjuvant therapy, rather than definitive chemoradiation, was recommended to this patient.



	Date		Mar-29	Mar-7	Mar-27
Plasma tumor markers levels	CEA (ng/mL)	Reference range: 0–5	34.11	5.39	2.03
	CyFra21-1 (ng/mL)	Reference range: 0–5	31.21	2.87	1.77
	NSE (ng/mL)	Reference range: 0–25	28.86	15.15	14.29
	SCC (ng/mL)	Reference range: 0–1.5	0.6	0.5	0.5
	CA125 (U/mL)	Reference range: 0–35	9.87	10.76	9.94

Figure 3 Plasma tumor markers levels during neoadjuvant chemo-immunotherapy. The plasma levels of the tumor markers CEA, CyFra21-1, and NSE were elevated at the time of initial diagnosis. All of them had decreased to normal levels after the first cycle of neoadjuvant chemo-immunotherapy and continued decreasing after the second cycle of neoadjuvant treatment. The plasma levels of the tumor markers SCC and CA125 were normal and stable during the neoadjuvant treatment period. RR, reference range.

Previous studies have demonstrated that elevated levels of PD-L1+ lung cancer cells and tumor-associated immune cells after neoadjuvant chemotherapy generate a favorable response to immunotherapy (7). These results encourage the combination of chemotherapy and immunotherapy in neoadjuvant therapy for locally advanced NSCLC.

The timing of additional adjuvant immunotherapy presents a couple of interesting questions. Firstly, the best strategy for delivering additional adjuvant immunotherapy remains unclear. Based on limited preliminary clinical evidence, this patient was recommended to undergo additional adjuvant immunotherapy. Secondly, liquid biopsy of immunological markers, such as T cell clonal dynamics and $CD8^+$ T cell subsets, should be a focus of exploratory research (8,9).

Conclusions

Our case study suggests that immuno-based therapeutic strategies present alternative options for patients with initially unresectable locally advanced NSCLC with T4 or bulky swollen N2 lymph nodes.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at: http://dx.doi.org/10.21037/tlcr-20-517

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tlcr-20-517). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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