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Durvalumab may be an effective option for ALK positive patients with locally advanced NSCLC after concurrent chemoradiotherapy: A case report

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Abstract

An ongoing dilemma in the management of patients with unresectable locally advanced Non-small cell lung cancer (LA-NSCLC) is the management of patients with EGFR or ALK-postive adenocarcinomas. Anti–PD-L1/PD-1-based immunotherapy (ICI) as treatment for cancer has attracted an increased focus. Concurrent chemoradiotherapy (cCRT) followed by durvalumab (a checkpoint inhibitor that blocks the binding of PD-1 with PD-L1) as a consolidation therapy has been the standard treatment for patients with inoperable LA-NSCLC. However, the data of ICI therapy in ALK+ Stage III NSCLC is limited. Here, we present a patient with inoperable stage III NSCLC who received cCRT, achieved partial response after definitive chemoradiotherapy. Then with immunotherapy with durvalumab for consolidation, she quickly achieved complete response. Ultimately, this case reminds us that durvalumab may be an effective option for ALK positive patients with locally advanced NSCLC after concurrent chemoradiotherapy.

Keywords

Case report; ALK-positive; Non-small cell lung cancer; Durvalumab.

Introduction

Non-small cell lung cancer (NSCLC) makes up approximately 85% of lung cancer cases. Among these, rearrangement in Anaplastic lymphoma kinase (ALK), which results in dysregulation and incorrect signaling through the ALK kinase domain [1] occurs in 3%–5% of NSCLC patients [2,3]. The advent of ALK tyrosine kinase inhibitors (TKIs) therapy has dramatically improved survival times for patients with stage IV ALK+ NSCLC, with a median overall survival (OS) rate of up to 7.5 years reported for sequential ALK TKI

use [4]. Although Therapy with immune-checkpoint inhibitors (ICIs) is a treatment option in NSCLC, the efficacy of ICI is inconclusive in ALK+ Stage III NSCLC due to limited data. After the PACIFIC trial [5] was reported cCRT followed by durvalumab as consolidation immunotherapy became the standard treatment for patients with unresectable stage III NSCLC.

However, there wasn't ALK+ patient in the PACIFIC trial. And Real-world effectiveness (rwPFS) of ICIs in ALK+ NSCLC patients is relative lack. We present the following case in a patient with unresectable stage III ALk+ NSLCLC who achieved PR after a definitive chemoradiotherapy. Then with immunotherapy with durvalumab for consolidation, she quickly achieved Complete Response (CR).

Case Presentation

In Augest 2019, a 31-year-old woman visited our hospital with be found a mass in right upper lobe of lung by chest CT during medical examination. Measurements of serum tumour markers indicated elevated levels of neuron-specific enolase (NSE: 13.18 ng/mL, reference: ≤4.7 ng/mL), cytokeratin 19 fragment (Cyfra211: 2.88 ng/mL, reference: ≤3.3 ng/mL), and carcinoembryonic antigen (CEA: 1.22 ng/mL, reference: ≤4.7 ng/mL). An enhanced Computed Tomography (CT) of the chest and positron emission to-mography-computed tomography (PET-CT) showed a 1.3 × 1.0 cm cavity mass in the anterior segment (SUV 3.8) of the upper lobe of the right lung and right supraclavicular (1R) and mediastinal enlarged lymph nodes (4R), with the largest node being about 1 cm (SUV 4.7) (Figure 1A). There were no obvious metastases based on magnetic resonance imaging (MRI) of the brain and enhanced CT of the abdomen. The results of a right supraclavicular lymph node biopsy suggested the presence of a lung adenocarcinoma.

Immunohistochemical staining showed positive staining for CK, TTF-1, NapsinA and CK7, PD-L1 (+60% tumour cells), and negative staining for CK5/6, P40, SyN, CD56-, and P40. Molecular analysis indicated ALK rearrangement. No EGFR mutation or ROS1 fusion. Based on the 8th edition of the AJCC TNM staging system, we diagnosed the patient with locally advanced lung adenocarcinoma (cT1bN3M0, IIIB).

From 3 September 2019 to 12 September 2019 the patient received stereotactic body radiation therapy (SBRT) consisted of 50 Gy in 5 fractions on Planning Target Volume (PTV) of tumor lesion in the right upper lung. The Gross Tumor Volume (GTV) in the right upper lung was delineated on the 3DCT images. IGTV was contoured on the 4DCT MIP scans. ITV was generated by combining of GTV and IGTV. Planning Target Volume (PTV) had to be created to account for both set-up error and error related to motion followed by a 5 mm circumferential ITV expansion. GTV of lymph nodes (GTVnd) was defined as the volume of lymph nodes in the right supraclavicular and mediastinum (1R/4R). CTVnd was defined based on the principles of involved-field RT. Clinical target volume (CTVnd) was defined as the GTVnd with a 5 mm expansion, and the regions of 2R, 4R. Planning target volume (PTVnd) was defined as CTVnd with a 5 mm margin. Planning GTV (PGTVnd) was defined as GTVnd with a 5-mm expansion. From 11 September to 28 October 2019, 95% of PGTVnd received 61.2 Gy/1.8 Gy/34F and 95% of PTVnd received 50.4 Gy/1.8 Gy/28 F. The mean dose to the lungs (MLD) was 8.63 Gy.

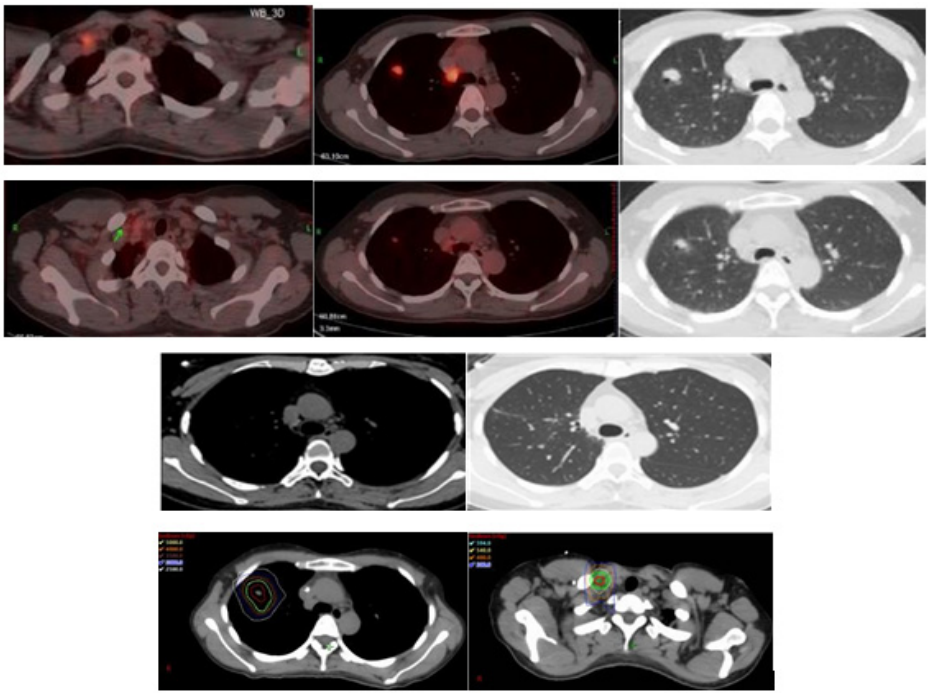

Figure 1: Radiotherapy volumes and dose distribution; the green line represents PTV and the red line represents GTV. PTV, planning target volume; GTV, gross tumor volume.

The percentage of lung volume that received a dose in excess of 5 Gy (V5), 20 Gy (V20), was 31.6% and 14.7%, respectively. The maximal dose to the Cord was 44.32 Gy. And two cyles of concurrent chemotherapy consisting of pemetrexed (500 mg/m^2, every 21 days) and cisplatin (75mg/m^2, every 21 days). The toxicities reported during cCRT included a decrease in white blood cells (grade I) based on the Common Terminology Criteria for Adverse Events (CTCAE) 4.0 criteria. After 1 month, PET/CT evaluation showed decreases in the sizes of the lung mass and lymph nodes, indicating a partial response (PR) (Figure 1B). Based on the NCCN guidelines, we recommended consolidation ICI-based immunotherapy. From 19 November 2019 to 8 July 2020, the patient had received durvalumab for a year and had no obvious treatment-related toxicities. CT scans in 15 December 2020 indicated clinical complete response (cCR) (Figure 1C). Radiotherapy volumes and dose distribution were as shown in Figure 1.

Discussion

Immunotherapy with programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors (ICIs), has demonstrated anti-tumor activity in NSCLC [6]. However, the majority of randomized controlled trials evaluating ICIs in patients with NSCLC have either excluded or included only a very limited number of ALK+ patients. Data on ICI use in ALK+NSCLC have been limited [6,7]. Impower 150, the only randomized controlled trial to specifically include a subgroup analysis of ALK+ NSCLC patients combined this subgroup (which represented only 3.3% of the total population) with a subgroup of patients whose tumors carried an epidermal growth factor receptor (EGFR) mutation; in this trial, the addition of the PD-L1 inhibitor atezolizumab to the combination of carboplatin/paclitaxel/bevacizumab resulted in a prolongation in both median progression-free survival (PFS) (9.7 months) and OS (not estimable) vs chemotherapy + bevacizumab (median PFS: 6.1 months; median OS: 17.5 months). However, these data are difficult to interpret and apply specifically to the ALK+ NSCLC patients as this subgroup of patients was small (N=13) and was

reported in conjunction with the EGFR -mutated patients, which likewise was a small subgroup [8]. And as patients with ALK + NSCLC have multiple ALK-targeted agents from which to choose. An ongoing dilemma in the management of patients with unresectable stage III NSCLC is the management of patients with EGFR or ALK+ carcinomas.

The response rate of ICIs alone is low, about 20% in non-selective populations. SBRT combined with ICIs treatment in NSCLC has achieved significant result [9]. Considering the tumor lesion in the anterior segment of the upper lobe of the right lung, we did not give the patient conventional cCRT with radiation-dose (60 Gy). Instead, SBRT radiotherapy was chosen to primary tumor lesion and radiation-dose (61.2 Gy) to involved field lymph nodes.

Durvalumab is a selective, high-affinity, human IgG1 monoclonal antibody, that binds to PD-L1 and blocks its interaction with PD-1 and cluster of differentiation (CD) 80 (B7.1). PD-L1 is expressed in a broad range of cancers. The binding of durvalumab to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells and allows T cells to recognize and kill tumor cell [10].

In this case, the patient started immunotherapy after ccRT and experienced no severe adverse events, which shows that durvalumab can be used safely soon after cCRT. A decrease in white blood cells and pneumonitis experienced by the patient were classified as grade 1 according to the CTC AE 4.0 criteria. From the data of PACIFIC trial [5], the use of durvalumab as consolidative immunotherapy does not increase the risk of any toxicity or pneumonitis.

Conclusions

To our knowledge, this is the first case report to describe the possible clinical efficacy of durvalumab for consolidation treatment of stage III ALK+ NSCLC patient. From this case, we found that the use of durvalumab following cCRT was feasible in a patient with ALK positive.

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