Complete response to pembrolizumab as a single agent in a patient with stage III NSCLC with high PD-L1 expression: a case report

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Abstract

Non-small cell lung cancer (NSCLC) accounts for 75-80% of all lung cancer cases. Stage III NSCLC represents a highly heterogenous stage characterized by different disease presentations and a wide range of treatment options. For patients with good performance status and unresectable-stage III NSCLC with programmed death-ligands 1 (PD-L1) tumor proportion score (TPS) ≥1%, durvalumab consolidation immunotherapy after a platinum-based chemo-radiotherapy is strongly recommended. However, age, poor performance status, underlying comorbidities may represent contraindications for chemotherapy to be used in a subgroup of patients. Herein, we report a case of an 80-year-old male affected by a stage IIIB lung adenocarcinoma with overexpression of PD-L1 (TPS 90%) treated with pembrolizumab, an immune checkpoint inhibitor targeting PD-1/PD-L1 pathways, which shows a complete resolution of lung lesion after four cycles of treatment. Although randomized controlled trials are required, this case report may suggest the potential role of pembrolizumab for chemotherapy unsuitable patients with overexpressing PD-L1 unresectable-stage III NSCLC.

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Introduction

Worldwide, lung cancer is the second most commonly diagnosed tumor with almost 2.2 million new cases and the leading cause of cancer related death, with nearly 1.8 million deaths [1]. NSCLC accounts for 75% to 80% of lung cancer cases, and most of these cases are locally advanced (stage III) or metastatic (stage IV) at the time of presentation [2,3]. Stage III NSCLC is highly heterogeneous with a wide spectrum of disease distribution and an equally complex range of treatment options. In general, the optimal treatment regimen is multimodal with systemic and local therapies for distant and local disease control, respectively [4]. An interdisciplinary approach is necessary to define multimodal treatment strategies based on patients' condition and disease extension [5,6]. Currently, patients with a good performance status and stage III (locally advanced) unresectable NSCLC receive a platinum-based chemotherapy administered with sequentially or concurrently definitive-dose radiotherapy [7]. The use of immune-checkpoint inhibitors (ICIs) targeting the PD-1 or PD-L1 signalling axis in the modulation of anti-tumor T-cell activity has revolutionised the treatment of both advanced NSCLC and SCLC [8,9]. In patients with advanced NSCLC and PD-L1 TPS of 50% or greater expression, the use of pembrolizumab, a humanized monoclonal antibody against PD-1, was associated with significantly longer progression-free and overall survival and with fewer adverse events than was platinum-based chemotherapy [10]. Immunotherapy has also been investigated in unresectable stage III NSCLC and it currently represents the therapeutic standard

based on the randomised control PACIFIC trial. Consolidation with durvalumab, a PD-L1 inhibitor, was associated with significant improvements in the primary endpoints of overall survival and progression free survival with manageable safety [11]. Nevertheless, tumor heterogeneity is considered the major cause of treatment failure in current cancer therapies [12]. Therefore, the evaluation of predictive biomarkers is essential for treatment decision making in advanced stage NSCLC and has shifted the treatment paradigm of NSCLC to more individualized therapy.

Case Report

An 80-year-old male with 60 pack-years smoking history was admitted to our Department complaining general malaise, persistent cough, exertional dyspnea and weight loss of about 8 kg in 8-10 weeks. His medical history included arterial hypertension, severe COPD, mild tricuspid and mitral insufficiency, moderate aortic insufficiency and previous right upper partial lobectomy for atypical adenomatous hyperplasia. Clinical examination showed Eastern Cooperative Oncology Group (ECOG) performance status (PS) 1-2. Computed tomography (CT) and positron emission tomography/computerized tomography (PET/CT) scans showed a 63 mm mass in the middle lobe of the right lung (SUV max 18.2) as well as secondary lymph nodes in prevascular, Barety, subcarinal and right hilar sites (SUV max 15.6) (Figure 1 A,B). The target lesion was indissociable from the vascular-bronchial structures, the costal pleura, the mediastinal one and from the fissure. CT findings suggested a clinical stage IIIB (cT3N2M0) NSCLC. He had undergone a bronchoscopy bronchial biopsy of the right middle lobe which had revealed the presence of lung adenocarcinoma. Molecular profiling did not detect any mutation in main drugable oncogene drivers including epidermal growth factor receptor (EGFR), BRAF, ROS1 and rearrangements of the anaplastic large-cell lymphoma kinase (ALK) gene whereas were identified Kirsten rat sarcoma viral oncogene homologue (KRAS) G12C mutation and a strong PD-L1 expression (TPS 90%) (Figure 1 E,F). Blood tests at diagnosis were within normal limits. The patient was received pembrolizumab 200 mg iv every 3 weeks; the decision has been made according to advanced age, comorbidities, the high risk of intolerance to chemotherapy and radiotherapy and the overexpression of PD-L1 (TPS 90%). After two cycles of systemic therapy, the patient experienced significant clinical improvement, with reduction of cough and dyspnea in the absence of the need for steroid therapy. At restaging, CT chest scans showed a complete resolution of lung lesion after four cycles of pembrolizumab, only some fibrotic striae remained in the same site and the lymphadenopathies in prevascular, Barety and subcarinal were stationary (Figure 1 C,D). The treatment was overall well tolerated; indeed, the continued pembrolizumab administration patient has experienced a significant clinical improvement with also weight gain. These early findings were corroborated from the following PET/CT scans documenting a complete response to pembrolizumab, after twelve treatment cycles. At the time this manuscript was submitted, the patient and remained on oncological follow-up. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

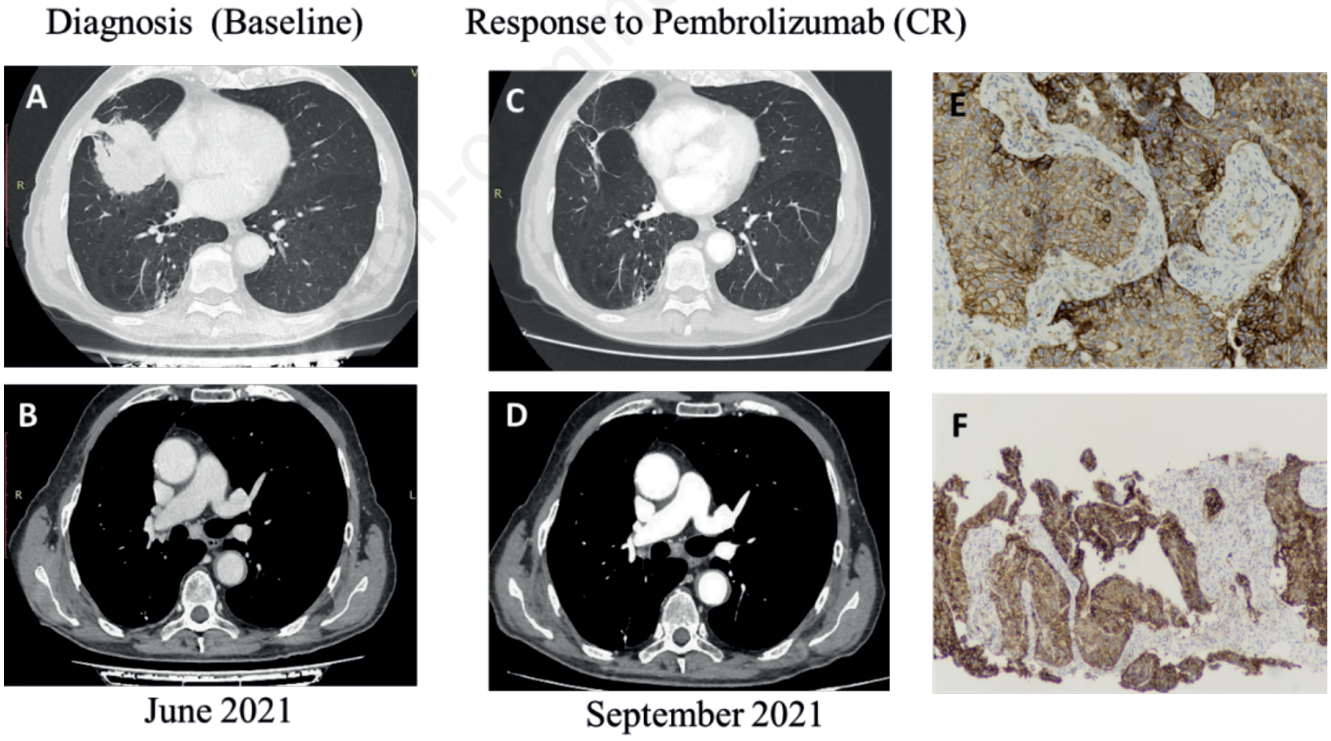

Figure 1. Computed tomography (CT) scans and of the thorax of the patient. A,B) CT scans at diagnosis (baseline) in June 2021. C,D) CT scans after four cycles of pembrolizumab in September 2021. E,F) Immunohistochemical examination: pathologic findings from the right middle lobe lesion at the time of diagnosis showed adenocarcinoma with positive immunohistochemical staining for PD-L1.

Discussion

Patients with locally advanced stage III NSCLC consist of a heterogeneous population; therefore, clinical management for these patients is complex and should be tailored on individual basis. The range of treatment approaches for these patients has changed over time [13]. In the late 1980s, radiotherapy was the standard treatment for patients with stage III NSCLC unresectable disease. Subsequently, phase III RCTs have shown a clear survival benefit with platinum-based combination chemotherapy administered with thoracic radiation as compared to radiation alone [14.] Recent advances in understanding complex interplay between cancer cells and immune checkpoint has revolutionized the standard treatment of patients with advanced lung cancer and more [15-17]. ICIs are antibodies that target key signaling pathways such as PD1/PD-L1 and 2 restoring the anti-tumor immune responses. As results of a growing body of the literature, immune checkpoints inhibition is actually the standard of care for locally advanced or metastatic NSCLC both in monotherapy or in combination with platinum-based doublets according to patients and cancer characteristics. In particular, for stage III unresectable NSCLC with PD-L1 TPS ≥1, the multimodal treatment strategy – including platinum-based chemo-radiotherapy followed from consolidation with durvalumab, a humanized monoclonal antibody targeting the PD-L1 is now the standard of care [7]. However, not all patients with locally advanced NSCLC can be treated with combination of chemotherapy and radiotherapy because of age, PS and comorbidities. Indeed, most pivotal clinical trials of chemoradiation did not include patients with ECOG PS 2 and patients aged 75 years or older.

Pembrolizumab, a humanized monoclonal antibody blocking PD-1 through PD-1/PDL1 pathway blockade, removes the suppressive effects of PD-L1 on cytotoxic T-cells with restoration of host immunity against the tumor, with increased antitumor activity in advanced NSCLC harboring PD-L1 expression on cancer cells [18,19]. Based on data from KEYNOTE-024 study, pembrolizumab monotherapy was approved from regulatory agencies as first-line treatment for metastatic NSCLC with high PD-L1 expression (TPS ≥50%) in absence of EGFR mutation or ALK translocation [10]. Many studies are based on prespecified subgroup analyses of different PD-L1 thresholds to determine which cut-point best predicts the effectiveness of pembrolizumab monotherapy [20]. According to a multicenter retrospective analysis [21], clinical outcomes were improved with increasing PD-L1 expression levels ≥75% and particularly ≥90%, among patients with NSCLC and a PD-L1 expression level ≥50% treated with first-line pembrolizumab. Compared with patients with PD-L1 expression of 50-89%, patients with an expression level of 90-100% had a significantly higher ORR (60.0% *versus* 32.7%, p<0.001), a significantly longer mPFS [14.5 *versus* 4.1 months, hazard ratio (HR) 0.50 and a significantly longer mOS [not reached *versus* 15.9 months, HR 0.39. This suggests that expression status of PD-L1, especially PD-L1 high expression levels, could explain the application of immunotherapy monotherapy. Moreover, Kilickap *et al.* reported the results of a post hoc analysis of the phase III EMPOWER-Lung 1 trial of a programmed cell death 1 inhibitor, cemiplimab in patients with treatment-naïve stage IIIB, IIIC, or IV NSCLC with PD-L1 of at least 50%. In this study, the first-line treatment with cemiplimab monotherapy significantly improved OS and PFS compared with a platinum-doublet chemotherapy in patients with advanced NSCLC whose tumors express PD-L1 in at least 50% of tumor cells. Particularly, clinical benefits were distributed according to PD-L1 expression levels, in patients with advanced NSCLC and PD-L1 expression, cemiplimab demonstrated greater improvements in survival and larger reductions in tumor volume in those with higher PD-L1 expression levels (TPS ≥90%). Notably, the study also included a proportion of patients with locally advanced non-small-cell lung cancer who were not candidates for definitive chemoradiation, and those with treated and clinically stable brain metastases. In particular, among patients in the cemiplimab arm, locally advanced NSCLC who received immunotherapy was represented by 45 (16%) patients with a PD-L1 TPS of 50% or greater [22]. This again suggests that expression status of PD-L1, especially PD-L1 TPS ≥90%, could be the most important measure condition of the application of immunotherapy. Furthermore, as the efficacy of ICIs is closely related to the tumor microenvironment, heterogeneous tumor microenvironments of various organs may potentially lead to a discrepant response to ICIs. Thus, information on PD-L1 expression in metastatic lesions and on the degree of concordance with primary tumors are particularly relevant for a correct evaluation. Indeed, tumors with local recurrence may exhibit a different profile in terms of PD-L1 expression, perhaps reflecting more complex and heterogeneous biological properties of neoplastic cells than primary tumors [23].

Therefore, beyond international guidelines based on clinical trials, therapeutic program for unresectable locally advanced disease should consider factors such as molecular pathology, age, PS and comorbidities. The majority of patients with stage III NSCLC are elderly patients, have a poor functional status and suffer too much disease-related weight loss, as well as other comorbidity conditions that often disqualify them from enrollment in most chemoradiation trials [24]. Our patient was ineligible for chemoradiation because of age and clinically relevant comorbidities and possible side effects. Indeed, ICIs has showed remarkable safety profile also in elderly patients. A pooled analysis of safety and efficacy from the KEYNOTE-010, KEYNOTE-024 and KEYNOTE-042 studies conducted in patients older ≥75 years documented fewer treatment-related adverse events (AEs) in elderly patients (overall, 68.5% *vs* 94.3%; grade ≥3, 24.2% *vs* 61.0%) when compared with standard chemotherapy [25]. In conclusion, this case report suggests that pembrolizumab can be effectively useful in this patient population and it emphasizes the importance of a PD-L1 cut point oriented treatment in the elderly patients. Although more study is required, pembrolizumab monotherapy may be an effective treatment for Stage III NSCLC and PD-L1 TPS ≥90%. Subgroup analyses of different PD-L1 cut points to determine which threshold best predicts the effectiveness of pembrolizumab monotherapy are necessary.

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