Small cell lung cancer (SCLC) is characterized by rapidly progressing tumor with poor survival. [1] Immuno-therapy is a novel approach that targets patient’s own immune system to enhance antitumoral response. Immune checkpoint inhibitors (CPI), are available and had modest activity for SCLC. [2] The antiPDL1 antibody atezolizumab with combination of carboplatin and etoposide in the first line treatment of SCLC improve survival nearly 2 months. [2] CPI related neurological side effects are rare but they can be lethal. [3] They manifest in dose dependent manner within 3-12 months of initiation of therapy with incidence of ≥ grade 3 adverse effect was <1%. [4] After nivolumab therapy myastenic crisis was reported in melanoma patient. [3] Immune mediated toxicities, paraneoplastic disorders such as Lambert-Eaton myasthenic syndrome (LEMS) resulting from reactivation of immune system are elicited by blockage of immune checkpoints. [5] In the differential diagnosis cranial metastasis and paraneoplastic syndromes should be thought. [3] In the case of myastenia gravis CPI should be withheld, systemic corticosteroid, and pyridostigmine and iv-ig therapy. The number of the patient that treated with immunotherapy will increase in the future so it should be important to know the adverse effects management of immunotherapy.

Keywords: Myastenia gravis, atezolizumab, immunotherapy

Case Report

Myastenic Syndrome Diagnosed After Treatment of Small Cell Lung Cancer with Atezolizumab (PDL-1 Inhibitor)

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Abstract

Immune checkpoint inhibitors have been increasingly used for many type of solid tumor; first line treatment of small cell lung cancer (SCLC) with chemotherapy combination with atezolizumab is one of them. Although usually well tolerated, autoimmune related side effects can be seen. We report of autoimmune myastenia gravis that occurred after treatment of atezolizumab, an anti-programmed-death (anti-PD-1) monoclonal antibody.

Our patient is 71 year old woman with extensive stage small cell lung cancer receiving chemotherapy combined with atezolizumab. Although good oncological response to treatment after 8 cycle of atezolizumab, myastenia gravis was occurred. This autonimmune neurological syndrome is likely associated with atezolizumab treatment, patient had no any neurological disorder before. Symptoms were partially responded after steroid, piridostigmine and iv-ig therapy. The number of the patient that treated with immunotherapy will increase in the future so it should be important to know the adverse effects management of immunotherapy.

Keywords: Myastenia gravis, atezolizumab, immunotherapy

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that treated with immunotherapy will increase in the future so it should be important to know the adverse effects management of immunotherapy.[6]

Case Report

71 year-old woman was presented with supraclavicular lymph node metastasis. PET-CT revealed multiple bone, liver, mediastinal lymph nodes metastasis and right hiler mass. cranial MR showed clivus metastasis. SCLC with synaptophysin, chromogranin and TTF-1 positivity was diagnosed by biopsy from the supraclavicular lymph node. There was past medical history of hypertension, and colon cancer operation 20 years ago. There was neither history of autoimmune disorders nor corticosteroid dependence. She had 60 package year of smoking history. Standart carboplatin AUC5, etoposide(100mg/m²) and atezolizumab(1200mg/m²) and zoledronic acid 4 mg were started for every 3 weeks after palliative bone and cranial radiotherapy were performed. Atezolizumab maintenance for every 3 weeks was followed by 4 cycles of chemotherapy. Becuse of transaminise elevation (AST/ALT:255/212) atezolizumab was stopped during 8ᵗʰ cycle. Cholestasis tests, hepatitis markers (HbsAg, antiHCV, anti-HBc Igm, antiCMV), autoimmune hepatitis markers (ANA, ASMA, antiLKM) were negative, abdominal USG was normal. Immunotherapy related hepatitis was considered and methylprednisolone 1mg/kg was started. Over the 1 week, transaminases returned normal but she had complain of jaw pain, progressively increased dysphagia both for liquid and solid. bilateral ptosis, lower limb muscle weakness. Gastroscopy was normal, thoraco- abdominal CT and nasopharyngeal MR were normal and tumor had stabile clivus metastasis without any cranial nerve invasion; biochemical and cytological examination of lumbar puncture were normal. Repetitive nerve stimulation test was undiagnostic. Paraneoplastic panel including anti-Hu, anti-Ri, anti-Yo, antivoltage-gated potassium and calcium channel antibodies,acetylcholine receptor antibody were negative, but anti-titin antibody was positive. Myastenic symptoms developed during the 2⁴ᵗʰ week of atezolizumab treatment (after 8ᵗʰ cycle) and decreased after steroid, piridostigmine and ivig treatment after 2 months. She was extubated, swallowing and muscle weakness were gradually improved and she is still internalized for palliative rehabilitation care unit for 3 months after the start of steroid therapy without lung cancer exacerbation.

Discussion

Immunotherapy is increasingly used in solid tumor with better quality of life, lower side effect and longer survival compared to chemotherapy. Adverse effects are related with immunotherapy are different from the systemic chemotherapy.[7] Neurological adverse effects under anti-PDL-1 treatment were reported as nearly 10% with 0.1-15% of grade 3-4.[6] Although rare, they may lead to fatal consequences so it is important to diagnose and treat early. [6] Differantial diagnosis should always be performed because neurological symptoms can be related with infectious, paraneoplastic, vascular, toxic or metabolic causes. [6] Cerebrospinal fluid examination with cytology, culture or biochemical analysis support metastasis, infection or inflammatory mediated disease, cranial MRI can exclude new metastasis.[6]

Myastenia gravis is one of the neurological autoimmune syndrome characterized with proximal muscle weakness, ptosis, respiratory failure with isvolvement of respiratory muscle[6] is seen during therapy with CPI and 6.1% with anti-PD1 antibodies.[7] In addition to the clinical presentation, the repetitive nerve stimulation test, autoimmune antibody support the diagnosis of myastenic syndrome. In our case, only anti-titin antibody was positive that is similar to the pembrolizumab induced myastenia gravis in treatment of lung adenocarcinoma.[9] This antibody is generally positive in thymoma and late onset myastenia gravis and combined with poor prognosis.[10]

This syndrome was reported during treatment with nivolumab both for melanoma, SCLC and squamous cell lung cancer.[7] Although myastenia gravis related with anti-CTLA-4 or anti-PD1 have been reported, this case is noteworthy because it is the first reported to be related with atezolizumab, anti-PDL-1 antibody was used for SCLC. No eligible study related with neurological adverse effects of atezolizumab have been found in the literature. Abdel-Rahman and et al evaluated neurological toxicity of immunotherapy among 18 trials and 17 case reports of cancer patients.[6] Among 22 patients with neurological toxicity, only one had SCLC and none of them was taken atezolizumab.[8]

It was difficult to differantiate etiology as paraneoplastic syndrome or immune adverse effect. Because the onset of this syndrome developed after SCLC received nearly complete response clinically after atezolizumab therapy (6 months later), unlike paraneoplastic syndrome. Because later usually starts before diagnosis of malign disease and generally patient has symptom relief while primary disease was improved with therapy. Early recognition and can reverse the neurological symptoms within 6-12 weeks. [6] In our case the respiratory and proximal muscle weak-
ness reversed after 2 months. Systemic myastenia gravis can potentially life threatening syndrome with respiratory muscle involvement. It is difficult to predict whether continuation of immunotherapy may cause progression of myastenia gravis or not. Our patient also had radiologically nearly complete response to atezolizumab for 3 months without therapy. It is important to keep in mind that unexpected immune related adverse effects can be seen during treatment with CPI. Clinical suspicion and early treatment of this life-threatening adverse effect are important because autoimmune antibodies are not always clinically positive for differential diagnosis.

Disclosures

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

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Conflict of Interest: None declared.


References


