Immunotherapy-related toxicity in lung cancer: clinical characteristics and managing strategy

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Worldwide, lung cancer is the most common malignancy and the leading cause of cancer-related death. After the era of chemotherapy, radiotherapy, and molecular-targeted therapy, the treatment of advanced lung cancer has entered a new era of immunotherapy, represented by immune checkpoint inhibitors (ICIs), including programmed cell death protein-1/programmed cell death protein ligand-1 (PD-1/PD-L1) inhibitors and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) inhibitors.[1] However, patients treated with ICIs may experience unexpected systemic toxicities, some fatal. Thus, managing immunotherapy-related toxicity has become increasingly significant in patients with lung cancer. Here, we review the latest developments on the clinical features and management of immunotherapy-related toxicity in patients with lung cancer in order to promote the standardization of immunotherapy for lung cancer.

Clinical characteristics of immunotherapy-related toxicity

The toxicities can occur in almost every tissues and organs throughout the body, including skin, endocrine system, liver, gastrointestinal tract, lung, cardiovascular system, musculoskeletal system, nervous system, eyes, hematologic system, etc. In the present review, we mainly focus on several common or fatal toxicities.

Digestive toxicity

The digestive system is one of the most common sites affected by ICIs; and digestive toxicities mainly manifest with hepatic toxicity (hepatitis) and gastrointestinal toxicity (diarrhea and colitis).[2,3] In clinical trials of PD-1/PD-L1 inhibitors, the incidences of any-grade hepatic and gastrointestinal toxicities range from 2–9% and 1–15%, respectively; and those of grade 3 or higher are <1–4% and <1–3%, respectively.[4–12] Notably, gastrointestinal toxicity is frequently observed in patients with CTLA-4 inhibitors other than PD-1/PD-L1 inhibitors; moreover, ICI combination may significantly increase the possibility. A meta-analysis of incidence of immunotherapy-related colitis in various solid cancers revealed that no significant differences in gastrointestinal toxicity incidences were observed among different cancers (eg, melanoma, non-small cell lung cancer [NSCLC], renal cell cancer [RCC]). Incidence of all-grade colitis with CTLA inhibitor monotherapy and PD-1/PD-L1 inhibitor monotherapy were 9.1% and 1.3%, respectively. Patients receiving ICI combination (ipilimumab plus nivolumab) had the highest rate of all-grade colitis (13.6%).[13]

Endocrine toxicity

The most common endocrine toxicity is thyroid dysfunction (hypothyroidism and hyperthyroidism). Other endocrine toxicities have also been reported, such as thyroiditis, hypophysitis, type one diabetes and primary adrenal insufficiency, but they are rare.[2,3] Specific regimens appear to be associated with specific endocrine toxicities. Thyroid dysfunction is seen more commonly with PD-1/ PD-L1 inhibitors, whereas hypophysitis is seen more commonly with CTLA-4 inhibitors.[14] Following treatment of PD-1/PD-L1 inhibitors, 4–11% and 1–8% of patients with lung cancer experience any-grade hypothyroidism and hyperthyroidism, respectively; yet those of grade 3 or higher are rare (<1% for both).[4–11]

Pulmonary toxicity

Pulmonary toxicity is relatively common in lung cancer compared with other cancers; and it is the leading cause of immunotherapy-related deaths in lung cancer.[15] According to the preexisting clinical trials in patients with lung cancer treated with PD-1/PD-L1 inhibitors monotherapy,

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the incidence of any-grade pneumonitis ranges from 3% and 9%; and 1–3% of patients experience pneumonitis of grade 3 or higher.[4-12] Retrospective analyses suggest that old age (≥70 years), Asian ethnicity, former/current smoking status, squamous cell histological type, preexisting chronic lung disease (such as interstitial lung disease, chronic obstructive pulmonary disease [COPD]), combination therapy (PD-1/PD-L1 inhibitor plus CTLA-4 inhibitor, epidermal growth factor receptor-tyrosine kinase inhibitor plus PD-1/PD-L1 inhibitor) are associated with increased risk of pneumonitis.[13-18] On CT images, the radiologic features of pneumonitis are classified into four patterns: cryptogenic organizing pneumonia (COP), hypersensitivity pneumonitis (HP), acute interstitial pneumonia/acute respiratory distress syndrome (AIP/ARDS), and non-specific interstitial pneumonia (NSIP).[20]

Cardiovascular toxicities

Cardiovascular toxicity is rare in lung cancer, but it is highly lethal. Cardiovascular toxicities reported with ICI s in lung cancer include cardiomyopathy (mainly myocarditis), pericardial disease, arrhythmia, acute coronary syndrome, vascular disease and valve disease.[21] In a large-scale meta-analysis of fatal toxicities in cancers (including lung cancer), the mortality rate of myocarditis is up to 40%.[22] According to a recent real-world study, female, old age (≥75 years), and ICIs combination (ipilimumab plus nivolumab) may favor the occurrence of myocarditis.[23]

Management of immunotherapy-related toxicity

To date, several authoritative organizations have issued guidelines/consensus for immunotherapy; and the principles for management are comprehensive understanding, early recognition, timely detection, detailed assessment and effective management.[2,3,24-26] Before starting treatment, clinicians need to identify whether patients have underlying diseases or risk factors, including (1) pregnancy; (2) hepatitis B or C virus infection, human immunodeficiency virus (HIV) infection, or advanced age; (3) autoimmune diseases, hematopoietic stem cell transplantation or organ transplantation; and (4) poor general condition.[3] Pretreating laboratory tests such as complete blood count with differential, infectious disease screening panel, comprehensive metabolic panel; as well as imaging including CT scans of the chest, abdomen, and pelvis and echocardiography should be reviewed as baseline data.[3,12] Baseline data will be used as a reference for any abnormality occurring during immunotherapy.

During and after the immunotherapy, any adverse events should be assessed for three potential causes: disease progression, an unforeseen event, or an immunotherapy-related toxicity.[18] The differential diagnosis can be based on clinical manifestations, laboratory tests, and endoscopy and imaging examination. Test results should always be compared with baseline to detect any changes over time. Once diagnosed with immunotherapy-related toxicity, it should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) standard, and treatment should be tailored to different grades.[2,12,19,20] (1) Grade one toxicity does not require hospitalization, and immunotherapy may continue. The use of corticosteroids or other immunosuppressants is usually not recommended. (2) Grade 2 toxicity also does not require hospitalization, but immunotherapy should be suspended temporarily. Patients can be treated with topical or systemic glucocorticoids. (3) Grade 3 toxicity requires hospitalization and suspension of immunotherapy. Systemic glucocorticoid treatment is usually suggested. (4) Grade 4 toxicity requires hospitalization, and shall be considered for admission to intensive care unit. ICI therapy is permanently discontinued. Apart from systemic glucocorticoid, intravenous immunoglobulin is also suggested. Notably, for patients with grade 3 or 4 toxicity, whose symptoms do not subside after 3 to 5 days of treatment, other immunosuppressive therapy (anti-tumor necrosis factor α antibody, alpha-4 beta-7 integrin inhibitors, mycophenolate-containing medicines, etc) may be considered under the guidance of a specialist.

Prospect

Immunotherapy has provided a powerful and promising tool in the treatment of advanced lung cancer. However, there are still some issues to be explored. First, how to identify risk factors for developing specific immunotherapy-related toxicity after treatment with ICIs, which would contribute to the identification of susceptible population and the early diagnosis of toxicity. Second, more attention should be paid to the incidence and features of immune-related toxicities in the extension of immunotherapy (such as combination of ICIs and tyrosine kinase inhibitors). Third, more studies are needed to explore the characteristics of immune-related toxicities in the Chinese population, as most of the current clinical trials have been conducted in Europe and the United States. In summary, we need to develop a more reasonable whole-course management program for the lung cancer patients receiving immunotherapy.

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Conflicts of interest

None.

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