Lung cancer treatment in the era of immunotherapy

Yang Xu, Liang-An Chen

Department of Respiratory Diseases, The First Medical Center, The General Hospital of People's Liberation Army, Beijing 100853, China.

Lung cancer is among the most common malignant tumors that cause serious harm to humans. Despite the successes of chemotherapy, radiotherapy, and targeted therapy, the prognosis of lung cancer remains unsatisfactory. Fortunately, patients with lung cancer have found hope in immunotherapy, particularly, in immune checkpoint inhibitors (ICIs). ICIs are monoclonal antibodies that work against immune checkpoints, thus blocking the negative co-stimulation signaling pathway of T lymphocytes, restoring the body's anti-tumor immune response, and promoting the clearance of tumor cells. Common ICIs include programmed cell death (PD)-1 inhibitors (nivolumab and pembrolizumab), PD-ligand 1 (PD-L1) inhibitors (atezolizumab and durvalumab), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors (ipilimumab and tremelimumab).

Immunotherapy from Back-line Treatment to Neoadjuvant Therapy

Well-known ICI studies such as the CheckMate 017,[1] CheckMate 057,[2] KEYNOTE 010,[3] and OAK[4] studies have confirmed that compared with chemotherapy, ICIs improved the objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) of patients. The updated data of the CheckMate 017/CheckMate 057 studies published at the 2019 World Conference on Lung Cancer showed that the 5-year survival rate of patients in the ICIs group was significantly improved and that with immunotherapy, patients can achieve long-term survival. Nivolumab, pembrolizumab, and atezolizumab are recommended by the National Comprehensive Cancer Network (NCCN) guideline (category 1) for the second-line treatment of patients with non-small-cell lung cancer (NSCLC). Moreover, immunotherapy was also effective for second-line treatment of small cell lung cancer (SCLC). For instance, in the Checkmate 032 study,[5] patients with recurrent SCLC had a prolonged survival time after treatment with nivolumab, either alone or in combination with ipilimumab. Furthermore, patients with advanced SCLC also can benefit from pembrolizumab, as shown in the Keynote 028 and Keynote 158 studies. Immunotherapy has therefore changed the model of second-line treatment for lung cancer.

ICIs are effective not only in the second-line treatment of lung cancer, but also as first-line treatments. KEYNOTE 024[6] showed that first-line treatment with pembrolizumab for patients with high PD-L1 expression (PD-L1 ≥50%) resulted in better ORR and PFS than the standard first-line platinum-based chemotherapy. Recently, the 3-year follow-up survival data of KEYNOTE 024 indicated that the median OS of the first-line immunotherapy group was 26.3 months and that patients with high PD-L1 expression could have greater survival benefit. In contrast, the KEYNOTE 042 study was conducted to expand the applicable population for first-line immunotherapy. This study showed that compared with standard first-line platinum-based chemotherapy, first-line pembrolizumab treatment could prolong the OS of patients with NSCLC with PD-L1 expression ≥1%, whereas patients with PD-L1 expression ≥50% could benefit more.[7]

ICIs also extend to neoadjuvant therapy for early-stage NSCLC, in addition to advanced lung cancer. In CheckMate 159, a neoadjuvant study, patients with untreated stage I–IIIa resectable NSCLC were administered nivolumab for two cycles before surgery. The major pathologic response (MPR) of the patients reached 43%, and the treatment had been well tolerated without delaying the timing of surgery.[8] The updated data of CheckMate 159 presented at the 2019 American Society of Clinical Oncology Meeting showed that the median follow-up time was 34.6 months, whereas the median recurrent-free survival was not yet reached. In addition, the LCMC3, NADIM, MAC, and NEOSTAR studies all showed that immunotherapy was effective in the neoadjuvant treatment of early-stage NSCLC. These findings, therefore, indicate

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Correspondence to: Prof. Liang-An Chen, Department of Respiratory Diseases, The First Medical Center, The General Hospital of People's Liberation Army, Beijing 100853, China
E-Mail: chenla301@263.net

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that ICIs are feasible for pre-operative neoadjuvant therapy.

Immunotherapy from Monotherapy to Combination Treatment

After the breakthrough of immune monotherapy, researchers began to explore the feasibility of immune combination therapy to improve treatment efficacy. At present, the common regimens include ICIs combined with chemotherapy, radiotherapy, anti-angiogenic targeted therapy, and dual combination immunotherapy.

Chemotherapy and immunotherapy work synergistically, hence improving the immune effect. KEYNOTE 407, KEYNOTE 189, and IMpower 132 all showed that the combination of immunotherapy with chemotherapy was an effective first-line treatment strategy for advanced NSCLC without driver gene mutation. As for the first-line immunotherapy for SCLC, results of the IMpower 133, KEYNOTE 604, and CASPIAN studies showed that the combination regimen significantly prolonged the survival time of patients with SCLC. Therefore, the combination of chemotherapy and immunotherapy could also become the standard first-line treatment regimen for SCLC.

In contrast, radiotherapy can promote the release of tumor antigens and improve the immune response. The KEYNOTE 001[9] study showed that compared with pembrolizumab monotherapy, the PFS and OS of patients who underwent radiotherapy before immunotherapy were extended by 2.3 and 5.4 months, respectively.

Furthermore, drugs targeting anti-angiogenesis can inhibit tumor growth. The vascular endothelial growth factor (VEGF)/VEGF receptor pathway and the immune system can reportedly promote each other. The IMpower 150 study also showed that atezolizumab combined with bevacizumab and chemotherapy could prolong the OS of patients with lung cancer. Hence, atezolizumab combined with bevacizumab, carboplatin, and paclitaxel have been approved by the Food and Drug Administration for the first-line treatment of driver gene-negative non-squamous NSCLC.

Dual combination immunotherapy, such as the combination of CTLA-4 and PD-1/PD-L1 inhibitors, can enhance anti-tumor effects through complementary mechanisms. The CheckMate 012 and CheckMate 227 studies showed that nivolumab combined with ipilimumab had clinical benefits in the first-line treatment of patients with advanced NSCLC.[10,11] As lung cancer treatment methods improve, combined immunotherapy is gradually being recognized and will be the focus of future research.

Immunotherapy from Non-selective to Individualized Treatment

The development of ICIs has also promoted precision immunotherapy for lung cancer. Improving the efficacy of immunotherapy with precision medicine requires looking for biomarkers that can identify target beneficiaries of immunotherapy. For instance, several clinical trials have shown that the immunotherapy efficacy is correlated with PD-L1 expression. The NCCN guideline (category 1) recommends the detection of PD-L1 expression in patients with initially-treated advanced NSCLC. However, as a biomarker, PD-L1 still has limitations: the reagents for PD-L1 tests are diverse, interpretation of PD-L1 test results is subjective, and dynamic monitoring of PD-L1 is impossible.

Another biomarker is the tumor mutation burden (TMB), which has become popular with the rapid development of genome-wide sequencing technology.[12] CheckMate, POPLAR, OAK, and many other studies have suggested that TMB is correlated with immunotherapy efficacy. The 2019 NCCN guideline (category 2A) recommends the use of TMB to identify beneficiaries of the dual-agent immunotherapy with nivolumab plus ipilimumab and single-agent immunotherapy with nivolumab alone. However, insufficient evidence to support that TMB can predict the survival through immunotherapy, longer measurement period required, high-costs, and yet-to-be-set unified standards all contribute to TMBs' not being widely used as a biomarker.

Further research has also shown that other potential immunotherapy biomarkers include mismatch repair genes, microsatellite instability, tumor microenvironment, body immune status, and the intestinal flora composition.[13] This discovery of various predictive indicators hence promotes the development of individualized precision immunotherapy for lung cancer.

Development of Immunotherapy in China

While international immunotherapy drugs are being successively approved in China, domestic immunotherapy drugs are also being researched. On December 17, 2018, toripalimab was first approved by the National Medical Products Administration of China. Subsequently, sintilimab, camrelizumab, and tislelizumab were approved for marketing in China by the National Medical Products Administration. Currently, clinical trials on domestic ICIs for lung cancer therapy are being conducted, with some achieving excellent results. An umbrella phase II study included patients with advanced/metastatic NSCLC who were treated with camrelizumab as second-line treatment. This study reported that the ORR was 18.5%, which is comparable to the results of an imported PD-1 inhibitor second-line treatment. A phase III study in patients with advanced non-squamous NSCLC who had a negative driver gene treated with a combination regimen of camrelizumab and chemotherapy showed that compared with chemotherapy alone, the first-line combination treatment could significantly prolong the median PFS and median OS. Another phase III study in patients with advanced squamous cell lung carcinoma treated with tislelizumab showed that compared with chemotherapy alone, the PFS was significantly prolonged by first-line combination regimen of chemotherapy and tislelizumab. In addition to the second-line and first-line studies, domestic PD-1 inhibitors have also been used in neoadjuvant therapy. For instance, the MPR of patients with stage IA–IIIB NSCLC treated with sintilimab was up to 40.5%. The results from these studies, along with the

development of domestic PD-1 inhibitors by Chinese researchers, provide the basis for the potential of immunotherapy to treat patients with lung cancer in China.

Problems to be Solved in Immunotherapy

There are numerous problems to be considered in immunotherapy. ICIs can activate non-specific immune reactions, which lead to immunotherapy-related adverse reactions (irAEs).[14] The specific mechanisms of irAEs may include the following: (1) immunotherapy may activate some T cells and cause them to attack normal tissue cells; (2) the activated immune cells may increase the level of autoimmune antibodies and mediate an autoimmune reaction; and (3) the increase in anti-tumor activity leads to an increase in cytokines, which can damage normal tissues. Most irAEs are mild to moderate and can be controlled with temporary drug withdrawal or glucocorticoid therapy. With the widespread application of ICIs, serious irAEs have emerged, including immune-related pneumonitis, immune-related interstitial nephritis, and immune-related myocarditis. Checkpoint inhibitor pneumonitis (CIP) is a serious pulmonary toxicity associated with immunotherapy and a key cause of ICI-related death. The lung cancer group of the Chinese Thoracic Society has conducted a study and arrived at a consensus that will help clinicians identify and diagnose CIP and treat it effectively. Because of delayed and persistent immune response, some irAEs may appear late or even after drug withdrawal. Therefore, the prevention, identification, treatment, and follow-up monitoring of irAEs should be performed throughout the entire course of immunotherapy. Furthermore, similar to other anti-tumor drugs, drug resistance from immunotherapy could also develop. The drug-resistance patterns of immunotherapy can be divided into primary drug-resistance, adaptive drug-resistance, and acquired drug-resistance.[15] The mechanisms of drug resistance mainly involve three aspects: tumor cells, immune cells, and the tumor microenvironment. Immunotherapy drug resistance, formulation of individualized therapy, screening of optimal molecular biomarkers for immunotherapy, optimization of combined immunotherapy programs, and many other issues need to be further investigated and resolved.

ICIs in immunotherapy for lung cancer have shifted from back-line treatment to first-line treatment, from palliative treatment to consolidation treatment, from advanced lung cancer therapy to early neoadjuvant therapy, and towards precise individualized treatment. With the continuous development of treatment methods, combined immunotherapy is gradually being recognized, which could therefore benefit more patients. However, immunotherapy involves many problems that should be considered and resolved. We believe that with the gradual deepening of research, immunotherapy for lung cancer will bring more good news to lung cancer patients.

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Conflicts of interest

None.

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