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...

Correction to: Yang Xu, Liang-An Chen

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

DOI: 10.1097/CM9.0000000000001116

Access this article online

Quick Response Code:

Website: www.cmj.org

Copyright © 2020 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2020;133(20)

Received: 17-05-2020 Edited by: Pei-Fang Wei

2398
Immunotherapy for Lung Cancer. Improving the efficacy of immunotherapy for lung cancer. 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 mutations. 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 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. As lung cancer treatment methods improve, combined immunotherapy is gradually being recognized and will be the focus of future research.

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.[^13] 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.

**Funding**

This study was supported by a grant from the National Natural Science Foundation of China (No. 81902324).

**References**

1. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373:1627–1639. doi: 10.1056/NEJMoa1507643.
2. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373:133–143. doi: 10.1056/NEJMoa1504627.
3. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387:1540–1550. doi: 10.1016/S0140-6736(15)01281-7.
4. Rittmeyer A, Burris F, Waterkamp D, Park K, Cardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:235–246. doi: 10.1016/S0140-6736(16)3517-X.
5. Ready N, Farago AF, de Braud F, Atmaca A, Hellmann MD, Schneider JG, et al. Third-line nivolumab monotherapy in recurrent SCLC: CheckMate 032. J Thorac Oncol 2019;14:237–244. doi: 10.1016/j.jtho.2018.10.005.
6. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Cozzi T, Fulop A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016;375:1823–1833. doi: 10.1056/NEJMoa1606774.
7. Mok TSK, Wu YL, Kabuda I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019;393:1819–1830. doi: 10.1016/S0140-6736(18)32409-7.
8. Forde PM, Chaft JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. N Engl J Med 2018;378:1976–1986. doi: 10.1056/NEJMoa1716078.
9. Shaverdian N, Lisberg AE, Bornazyan K, Veruttipong D, Goldman JW, Formenti SC, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. Lancet Oncol 2017;18:895–903. doi: 10.1016/S1470-2045(17)30380-7.
10. Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 021): results of an open-label, phase 1, multicohort study. Lancet Oncol 2017;18:31–41. doi: 10.1016/S1470-2045(16)30264-4.
11. Hellmann MD, Gulden TE, Pluzanski A, Lee JS, Otterson GA, Audiger-Valette C, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 2018;378:2093–2104. doi: 10.1056/NEJMoa1801946.
12. Carbone DP, Reck M, Paz-Ares L, Cerehan R, Horn L, Steins M, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 2017;376:2415–2426. doi: 10.1056/NEJMoa1613493.
13. Gopalakrishnan V, Spencer CN, Neis L, Reuben A, Andrews MC, Karpinets TV, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science 2018;359:97–103. doi: 10.1126/science.aan4236.
14. Costa R, Carnero RA, Agudñik M, Rademaker AW, Pai SG, Villalor VM, et al. Toxicity profile of approved anti-PD-1 monoclonal antibodies in solid tumors: a systematic review and meta-analysis of randomized clinical trials. Oncotarget 2017;8:9519–9820. doi: 10.18632/oncotarget.13315.
15. Sharma P, Hui-Lieskovan S, Wargo JA. Primary, adaptive, and acquired resistance to cancer immunotherapy. Cell 2017;168:707–723. doi: 10.1016/j.cell.2017.01.017.

How to cite this article: Xu Y, Chen LA. Lung cancer treatment in the era of immunotherapy. Chin Med J 2020;133:2398–2400. doi: 10.1097/ CM9.000000000001116