ISSN 2618-1584 Vol. 4, Issue 8: 19-23, DOI: 10.25236/FMSR.2022.040805

Progress in Immunotherapy for Non-small Cell Lung Cancer

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Abstract: *The incidence rate and mortality of non-small cell lung cancer are increasing year by year. Some patients are not sensitive to traditional treatment. Today, with the arrival of the era of immunotherapy, the immunotherapy of non-small cell lung cancer is also progressing and developing. This paper mainly reviews the progress of immunotherapy of non-small cell lung cancer in recent years.*

Keywords: *Non-small cell lung cancer; Immunotherapy; Latest progress*

1. Introduction

Non-small cell lung cancer (NSCLC) is of major concern for society as it is associated with high mortality and is one of the most commonly occurring of all cancers. Due to the number of mutational variants and general heterogeneity of this type of cancer, treatment using conventional modalities has been challenging [1]. Therefore, it is important to have improved therapeutic treatments like immunotherapy, that can specifically treat the disease while causing minimal damage to healthy tissue and additionally provide systemic immunity. The emergence of immune checkpoint inhibitors has brought epic changes to the treatment of non-small cell lung cancer (NSCLC). In recent years, continuous adjustment and optimization have been made in perioperative period, local advanced stage and new combined treatment strategies. This paper briefly reviews the research progress of immunotherapy in lung cancer in recent years.

2. Progress of immunotherapy for perioperative NSCLC

New adjuvant immunotherapy related research is also in full swing. For example, in early resectable NSCLC, the primary remission rate (major pathological response, MPR) of neoadjuvant therapy for navuliewab; defined as residual tumor ≤ 10 %) up to 45 %, and TMB can predict the therapeutic response of navuliew monoclonal antibody, indicating that tumor genome plays a predictive role in early ICB treatment [2]. Neoadjuvant immunotherapy B has the potential advantage of contacting T cells and B cells with all tumor antigens, while tumor tissues have been resected or radiotherapy in adjuvant therapy, thus limiting the acquisition of tumor antigens [3].

Immunotherapy represented by immune checkpoint inhibitor (ICI) has gradually moved from late stage to early stage, opening a new milestone in the perioperative period of NSCLC [4]. Previous small sample studies showed that the MPR rate of ICI-based immunotherapy was about 14 % -45 %, and CheckMate-816 was the first phase III clinical study in the world to confirm that neoadjuvant immunotherapy can improve the pathological complete remission rate (pCR) of patients with resectable NSCLC. Results 1 in 2021 showed that the pCR (24.0 %: 2.2 %), MPR (36.9 %: 8.9 %) and ORR (54 %:37 %) of the combination chemotherapy regimen of navurizumab were better than those of the platinum-based dual-agent chemotherapy, and there was no increase in surgical complications. So far, we have seen its pCR result very bright, looking forward to its final EFS result. Domestic PD-1 monoclonal antibody also has related research, such as NeoTAP01 study 2 also showed the value of terripli monoclonal antibody combined with chemotherapy in neoadjuvant therapy of resectable stage III NSCLC, which adds a new choice for patients after surgery [5].

In the adjuvant immunotherapy of lung cancer, study 3 of IMpower010 was the first phase III clinical study to obtain positive results. The use of altizumab after adjuvant chemotherapy for stage II-III A NSCLC could significantly improve the benefit of DFS compared with the best supportive treatment (NE:

ISSN 2618-1584 Vol. 4, Issue 8: 19-23, DOI: 10.25236/FMSR.2022.040805

35.3 months, HR = 0.66). Based on this result, FDA approved altizumab for adjuvant therapy after surgery and platinum-containing chemotherapy for stage II-II A NSCLC patients with PD-L1 ≥ 1 %. This is also a new breakthrough in the treatment mode and strategy of early lung cancer [6].

The above two studies have determined the status of immunotherapy in the perioperative treatment of NSCLC, further improving the cure rate of early and medium-term lung cancer, but also bringing more thinking. Which treatment mode is better in perioperative period of NSCLC? To adopt the immune sequential surgery of CheckMate-816, or to adopt the immune sequential surgery of IMpower010, or to adopt the immune treatment strategy of the whole perioperative period. At present, there are ten studies on these three models are in full swing, I believe that there will be a clearer answer in the future [7].

3. Immunotherapy for advanced NSCLC

Although PD-1 single-agent immunotherapy has achieved good results in some patients, it is far from meeting clinical needs. The combination therapy strategy based on PD-1 monoclonal antibody has gradually achieved long survival and wide coverage in advanced NSCLC.

3.1. Combination chemotherapy

Immunotherapy combined with chemotherapy has been identified as the standard treatment for advanced NSCLC patients with driver gene negative. New follow-up data further confirm long-term survival benefits. The three-year OS data released by KeyNote-407 [8] study showed that no matter what the expression of PD-L1 was, the PFS (mPFS: 8.0 months vs 5.1 months, HR : 0.57) and OS (mOS: 17.2 months vs 11.6 months, HR: 0.71) time of patients in the pabolizumab combined with carboplatin + paclitaxel (albumin paclitaxel) group were significantly prolonged, and the three-year OS rates were 30 % and 18 %, respectively.GEMSTONE-302 [9] test, a total of 479 patients with newly diagnosed stage IV driver gene negative NSCLC were enrolled in the study. They were randomly treated with sulgrimab combined with paclitaxel / carboplatin (squamous cell carcinoma) or pemetrexed / carboplatin (non-squamous cell carcinoma) (n = 320) or placebo combined with chemotherapy (n = 159). The median PFS of sulgrimab group and control group was 9.0 months vs 4.9 months (HR 0.48, P < 0.0001), and the 12-month PFS rate was 36.4 % vs 14.8 %. The risk of progression or death was significantly reduced by 52 %, and the combination of sulgrimab and chemotherapy for NSCLC has been approved by the National Drug Administration (NMPA). CHOICE-01 (Treprivacizumab combined with chemotherapy), EMPOWER-Lung 3[10] (Cimprivacizumab combined with chemotherapy), CameL-sq [11] (Karelizumab combined with chemotherapy) and other studies of single-immunity combined with chemotherapy have also published the latest data this year, which consolidates the standard therapeutic status of immune combined with chemotherapy in patients with advanced NSCLC with negative drive genes.

3.2. Combined treatment of two immunotherapy drugs

The exploration of double immunotherapy for NSCLC is full of surprise and the prospect of first-line treatment is great. The 4 - year follow-up data of CheckMate-227 [12] study were updated. Compared with chemotherapy, no matter what the PD-L1 expression level of patients was, the combination of Navulizumab and low-dose Ipmab immunotherapy could bring lasting and long-term survival benefits. Among the patients with PD-L1≥1 %, the OS rate of 4 - year double-immune contrast chemotherapy was 29 % VS 18 %, HR = 0.76; in patients with PD-L1 < 1 %, the efficacy of double immunotherapy was more durable and in-depth, 24 % VS 10 %, HR = 0.64; enough to reflect the advantages of double immunotherapy for patients to chemotherapy provides options. Different from the study of CheckMate-227, the study of Checkmate-9LA [13] added short-term chemotherapy under the same immunotherapy scheme in order to bring about early disease control. This year, the OS data of two years were updated, and the results also maintained the same trend. Regardless of the expression of PD-L1, the OS of dual immunity combined with limited course of chemotherapy has benefited significantly. Compared with the two studies, the advantage of single immunotherapy is that the depth of treatment (CR rate) and breadth (DoR rate) are higher, and the short-term effect of chemotherapy (ORR rate) is better. 9LA also shows better efficacy in brain metastasis subgroup, mPFS is 13.5 months VS 4.6 months (HR = 0.36), and adverse reactions are controllable.

The POSEIDON [14] results of another study on PD-L1 monoclonal antibody combined with CTLA-4 monoclonal antibody were also published for the first time this year, and the first-line treatment of

ISSN 2618-1584 Vol. 4, Issue 8: 19-23, DOI: 10.25236/FMSR.2022.040805

patients with advanced NSCLC with dvacizumab combined with tremelimumab in four cycles of chemotherapy showed statistically significant improvements in PFS and OS, mPFS: 6.2 months VS 4.8 months, HR: 0.72; mOS: 14.0 months VS 11.7 months, HR 0.77.

The above three studies have shown that double immune combined / non-combined chemotherapy has its unique advantages, which brings more choices for the first-line treatment of patients with advanced NSCLC. At present, dual-immune drugs are available in China, and the clinical choice of which treatment mode can be individualized according to the patient's situation and needs.

3.3. Combined anti-vascular drugs

At present, it has been confirmed that anti-VEGF drugs have immunomodulatory effects, and targeted tumor angiogenesis combined with ICB treatment may become a feasible combination therapy. Bevacizumab (anti-VEGFA monoclonal antibody) can regulate immunosuppressive microenvironment, including myeloid inflammatory response thereby improving the activity of ICB [15.16]. Immunotherapy combined with chemotherapy combined with bevacizumab may improve the efficacy of NSCLC-related liver metastasis patients. However, whether the mechanism of this increase in efficacy is due to the regulation of immunosuppressive TME by bevacizumab or the normalization of tumor vessels remains to be further studied [17].

For NSCLC with EGFR / ALK-driven gene positive mutations, the efficacy of immunotherapy is poor, and combined treatment may break the deadlock. Relationship between EGFR mutation and PD-L1 expression EGFR is a receptor for epidermal growth factor (EGF) cell proliferation and signal transduction. EGFR pathway can regulate the expression of PD-L1 in NSCLC. In NSCLC cells, increasing EGFR kinase activity can activate the downstream related pathways and promote tumor occurrence. EGFR can affect tumorigenesis and development through MAPK / p-ERK1 / 2, ePI3K / Akt/ mTOR and IL-6 / JAK / STAT pathways [18].

Subgroup analysis of IMPOWER150[19] suggests that EGFR / ALK positive patients may benefit from the four-drug combination model. At this year 's ESMO conference, the results of our country-led ORIENT-31 study 9 's first mid-term analysis were heavily published. The results showed that the four-drug combination regimen significantly prolonged the median PFS (6.9 months vs 4.3 months) compared with standard chemotherapy, and significantly reduced the risk of disease progression by 54 %, which is undoubtedly a welcome news for our country 's large driver gene-positive patients.

However, positive results were not obtained in the first-line treatment of PD-L1 positive non-small cell lung cancer patients with parbolizumab combined with lenvatinib (LEAP-007) [20], and the mOS (14.1 months vs 16.4 months) and safety (57.9 % vs 24.4 %) of the combined group were inferior to those of the immune monotherapy group. In order to bring more doubts about the combination of antiangiogenic drugs, it is necessary to be cautious in formulating strategies.

Immunotherapy combined with TK I inhibitors can achieve good results in some driver gene-positive NSCLC patients, but whether immunotherapy combined with TK I inhibitors can increase the side effects is one of the problems that need attention. The side effects of immunotherapy combined with EGFR-TKIs in lung cancer have been reported. Immunotherapy combined with targeted therapy does not significantly increase the side effects, and patients can tolerate it. Only a few patients have serious adverse reactions [21]. In 2020 ASCO [22], the first prospective CT18 study in China for patients with EGFR mutation, i.e. stage I study of EGFR mutation-positive T790 M-negative advanced NSCLC patients with EGFR-TKI failure treated with terreprimab combined with chemotherapy, only 15 % of patients had chemotherapy-related nausea, vomiting, leukopenia and other adverse reactions.

3.4. Immunotherapy combined with radiotherapy and chemotherapy

Immunotherapy combined with chemotherapy can effectively improve cellular immune function in advanced NSCLC patients with high PD-L1 expression. The reason is that chemotherapy can cause different degrees of damage to patients' T lymphocytes, thereby affecting the immune function of the body. The application of Pembrolizumab can effectively reduce the damage caused by chemotherapy to patients' T lymphocyte subsets, promote the improvement of natural killer cell activity, and ultimately achieve the purpose of effectively maintaining the normal immune function of the body [23-24].

Immunoconsolidation therapy after concurrent chemoradiotherapy (CCRT) is still the standard treatment mode for locally advanced NSCLC recommended by major guidelines. The 5 - year follow-up data of PACIFIC [25] study were updated. The OS of 42.9 % of patients in the dulvariab group was more

ISSN 2618-1584 Vol. 4, Issue 8: 19-23, DOI: 10.25236/FMSR.2022.040805

than 5 years, and 1 / 3 of the patients were still in a state of progression-free survival in 5 years, achieving the best 5 - year survival data of lung cancer immunotherapy. The biggest advantage and characteristics of GEMSTONE-301 study are that in addition to concurrent chemoradiotherapy patients, 10, mPFS of sequential chemoradiotherapy patients were included: 9.0 months vs 5.8 months, HR 0.64; mOS: not reached vs 24.1 months, HR = 0.44. The positive results of this study suggested that sequential chemoradiotherapy + immunization was also an optional strategy. The model of concurrent chemoradiotherapy is also in full swing. The results of KEYNOTE-799 study show that, regardless of the expression of PD-L1 and tumor histology, concurrent chemoradiotherapy combined with parbolizumab has good safety and effectiveness, and the incidence of grade 3 pneumonia, one of the main research endpoints, meets the expectation (≤ 8 %).

4. Other joint strategies

Combination with new target drugs is a breakthrough treatment mode to further improve the effect of immunotherapy. LAG3 combined with PD-1 was first successful in melanoma. It suggested the possibility of combined treatment with inhibitors at different immune checkpoints. TROP-2-targeted antibody-coupled drug Dato-DXd combined with Papolizumab in patients with advanced NSCLC stage IB clinical research, T-DXd treatment of HER2mutation in patients with advanced NSCLC stage II clinical research DESTINY-Lung01, soluble LAG-3fusion protein Eftilagimodalpha combined with Papolizumab first-line treatment of NSCLC stage II clinical research are actively in progress. Expect these research data to bring us more surprises [27].

5. Conclusion

The focus of future research on non-small cell lung cancer is to continue to explore immunotherapy, optimize existing regimens and reduce the incidence of adverse reactions; indeed, in today 's era of precision therapy, how to accurately screen immune beneficiaries with multiple biomarkers, how to choose drug combination regimens, the timing of immunotherapy intervention, the setting of drug dose, and how to treat after immune resistance are still urgent problems to be solved.

Acknowledgements

Funding: Scientific Research Project of Shaanxi Provincial Administration of Traditional Chinese Medicine (2019-GJ-LC010)

References

[1] Jasmine K, Jackson E, L. MA, et al. Immunotherapy for Non-small Cell Lung Cancer (nsclc), as a Stand-alone and in Combination Therapy [J]. Critical Reviews in Oncology/hematology, 2021 (prepublish).

[2] Forde, P. M. et al. Neoadjuvant PD-1 blockade in resectable lung cancer. N. Engl [J]. Med. 378, 1976-1986 (2018).

[3] Zhang Ying, Chen Qian, Shi Yuxia, etc. Application progress of neoadjuvant immunotherapy in non-small cell lung cancer [J]. Anhui Medicine, 2022, 43 (2): 240-243.

[4] Sharma, P. et al. The next decade of immune checkpoint therapy. Cancer Discov. 11, 838-857 (2021).

[5] Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer [J]. N Engl J Med. 2022; 10.1056.

[6] Passiglia F, Bertaglia V, Reale ML, et al. Major breakthroughs in lung cancer adjuvant treatment: Looking beyond the horizon [J]. Cancer Treat Rev. 2021; 101 :102308.

[7] Bai R, Li L, Chen X, Chen N, Song W, Cui J. Neoadjuvant and Adjuvant Immunotherapy: Opening New Horizons for Patients with Early-Stage Non-small Cell Lung Cancer [J]. Front Oncol. 2020; 10: 575472. Published 2020 Oct 9.

[8] Cheng Y, Zhang L, Hu J, et al. Pembrolizumab Plus Chemotherapy for Chinese Patients with Metastatic Squamous NSCLC in KEYNOTE-407 [J]. JTO Clin Res Rep. 2021;2(10):100225. Published 2021 Sep 25.

[9] Zhou C, Wang Z, Sun Y, et al. Sugemalimab versus placebo, in combination with platinum-based chemotherapy, as first-line treatment of metastatic non-small-cell lung cancer (GEMSTONE-302): interim and final analyses of a double-blind, randomised, phase 3 clinical trial [J]. Lancet Oncol. 2022;

ISSN 2618-1584 Vol. 4, Issue 8: 19-23, DOI: 10.25236/FMSR.2022.040805

23(2): 220-233.
[10] Kuznik A, Smare C, Chen CI, et al. Cost-Effectiveness of Cemiplimab Versus Standard of Care in the United States for First-Line Treatment of Advanced Non-small Cell Lung Cancer with Programmed Death-Ligand 1 Expression ≥50 [J]. Value Health. 2022; 25(2): 203-214.
[11] Ren S, Chen J, Xu X, et al. Camrelizumab Plus Carboplatin and Paclitaxel as First-Line Treatment for Advanced Squamous NSCLC (CameL-Sq): A Phase 3 Trial [J]. J Thorac Oncol. 2022; 17(4): 544-557.
[12] O'Byrne KJ, Lee KH, Kim SW, et al. First-line nivolumab + ipilimumab in advanced NSCLC: CheckMate 227 subpopulation analyses in Asian patients [J]. ESMO Open. 2022; 7(1): 100394.
[13] Reck M, Ciulenua T-E, Cobo M, et al. First-line nivolumab (NIVO) plus ipilimumab (IPI) plus two cycles of chemotherapy (chemo) versus chemo alone (4 cycles) in patients with advanced non-small cell lung cancer (NSCLC): Two-year update from CheckMate 9LA. 2021 ASCO. Abstr 9000.
[14] Three-Drug Regimen Bests Chemo in NSCLC. Cancer Discov [J]. 2021; 11(11): OF2.
[15] Hegde, P. S., Wallin, J. J. & Mancao, C. Predictive markers of anti-VEGF and emerging role of angiogenesis inhibitors as immunotherapeutics. Semin. Cancer Biol. 52, 11 7-124 (2018).
[16] Oyama, T. et al. Vascular endothelial growth factor affects dendritic cell maturation through the inhibition of nuclear factor-kappa B activation in hemopoietic progenitor cells [J]. Immunol. 160, 1224-1232 (1998).
[17] Reck, M. et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. Lancet Respir. Med. 7, 387-401(2019)
[18] Sharma SV, Bell DW, Settleman J, et al. Epidermal grow th factor receptor mutations in lung cancer. Nat Rev Cancer, 2007, 7(3): 169-181.
[19] West HJ, McCleland M, Cappuzzo F, et al. Clinical efficacy of atezolizumab plus bevacizumab and chemotherapy in KRAS-mutated non-small cell lung cancer with STK11, KEAP1, or TP53 comutations: subgroup results from the phase III IMpower150 trial. J Immunother Cancer. 2022;10(2): e003027.
[20] Xue Y, Zheng K, Xue J. Immunotherapy with toripalimab for lung adenocarcinoma in a real-world patient with an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 4: a case report. Ann Palliat Med. 2021; 10(9): 10114-10123.
[21] Xing P, Wang M, Zhao J, et al. Study protocol: A single-arm, multicenter, phase II trial of camrelizumab plus apatinib for advanced nonsquamous NSCLC previously treated with first-line immunotherapy. Thorac Cancer, 2021, 12(20): 2825-2828.
[22] Jiang T, Wang P, Zhang J, et al. Toripalimab plus chemotherapy as second-line treatment in prev iously EGFR-TK I treated patients w it h EGF R-mut a nt-adv a nced NSC L C: a mu lt icenter pha se-II trial. Signal Transduct Target Ther, 2021, 6(1): 355.
[23] HSU P C, JABLONS D M, YANG C T, et al. Epidermal Growth Factor Receptor (EGFR) Pathway, Yes-Associated Protein (YAP) and the Regulation of Programmed Death-Ligand 1(PDL1) in Non-Small CellLung Cancer (NSCLC) [J]. Int J Mol Sci, 2019, 20(15): 3821-3822.
[24] LIU S Y, WU Y L. Tislelizumab: an investigational anti-PD-1 antibody for the treatment of advanced non-small cell lung cancer (NSCLC) [J]. Expert Opin Investig Drugs, 2020, 29(12): 1355-1364.
[25] Jazieh K, Khorrami M, Saad A, et al. Novel imaging biomarkers predict outcomes in stage III unresectable non-small cell lung cancer treated with chemoradiation and durvalumab. J Immunother Cancer. 2022;10(3): e003778.
[26] Jabbour SK, Lee KH, Frost N, et al. Pembrolizumab Plus Concurrent Chemoradiation Therapy in Patients with Unresectable, Locally Advanced, Stage III Non-Small Cell Lung Cancer: The Phase 2 KEYNOTE-799 Nonrandomized Trial [published online ahead of print, 2021 Jun 4]. JAMA Oncol. 2021; 7(9): 1-9.
[27] Wang N, Zhao L, Zhang D, Jia Y, Kong F. Zhongguo Fei Ai Za Zhi. 2022; 25(3): 214-218. doi: 10.3779/j.issn.1009-3419.2022.102.01