Review Article

Clinical status and perspective on the application of immunotherapy combined with chemotherapy in advanced non-small cell lung cancer: a review

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: T Wang; (V) Data analysis and interpretation: T Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: The therapeutic landscape of advanced non-small cell lung cancer (NSCLC) has been significantly improved by developing immunotherapy represented by programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) immune checkpoint inhibitors (ICI). Furthermore, immunotherapy combined with chemotherapy is an essential treatment strategy for driver-negative advanced NSCLC, especially in a population with PD-L1 <50%, and leads to long-term survival in the entire population regardless of the PD-L1 expression status. However, specific challenges must be overcome, including how to use immunotherapy with chemotherapy in clinics. Furthermore, the application of immunotherapy with chemotherapy in populations such as elderly patients and patients with brain metastases, oligometastases, epidermal growth factor receptor (*EGFR*) gene mutation, anaplastic lymphoma kinase (*ALK*) gene rearrangements, and other driver gene-positive populations must be further explored. The biomarkers associated with immunotherapy and chemotherapy are still unclear, and the search for predictive biomarkers can contribute toward more precise and personalized immunotherapy. Furthermore, treatment strategies after immunotherapy and chemotherapy resistance are of significant focus clinically, and clinical studies with multiple combination therapy strategies are ongoing. Therefore, based on the reported status of immunotherapy combined with chemotherapy for advanced NSCLC, this study conducted a comprehensive literature review by searching keywords "PD-1 and PD-L1, immune checkpoint inhibitor (ICI), and NSCLC" in MEDLINE, major conferences, and major clinical research projects to elucidate the therapeutic efficacy of immunotherapy combined with chemotherapy as the current first-line treatment approach for various types of NSCLC patients. Additionally, it addresses several pressing challenges associated with immunotherapy combined with chemotherapy, including enhancing treatment response and survival rate in specific patient populations and identifying potential biomarkers.

Keywords: Advanced non-small cell lung cancer (advanced NSCLC); immunochemotherapy; programmed cell death

Submitted Aug 29, 2023. Accepted for publication Mar 16, 2024. Published online Apr 07, 2024.
doi: 10.21037/cco-23-92
View this article at: https://dx.doi.org/10.21037/cco-23-92

Introduction

In recent years, the development of drugs represented by programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) inhibitors has reshaped the arena for treating lung cancer. In advanced non-small cell lung cancer (NSCLC), immunochemotherapy has made significant progress after successful results were obtained from immune monotherapy second-line and first-line treatment in a population with high expression of PD-L1 (1,2). Subsequently, immunochemotherapy became the most widely used clinical treatment strategy. With the approval of more than ten immune drugs and their combination chemotherapy worldwide, several drugs have been included in medical insurance to utilize the full potential of immunotherapy, generating more treatment options for patients and improving the survival of advanced NSCLC patients with negative driver genes. To further improve the curative effects of immunochemotherapy in advanced NSCLC patients and optimize the associated treatment strategies, several clinical challenges must be solved. For example, specific challenges include achieving a longer survival rate with immunochemotherapy, targeting special populations, applying immunochemotherapy in driver gene-positive populations, selecting treatment strategies after progression, and identifying predictive biomarkers that must be further explored. This review aims to elaborate on the reported therapeutic effects of immunochemotherapy in the aforementioned specific patient population comprehensively and summarize relevant issues that remain unresolved at this juncture, with the aim of bringing more precise and refined immunotherapy strategies for advanced NSCLC patients.

Search strategy and selection criteria

A comprehensive literature search was conducted including publications from MEDLINE database, major clinical research projects, and presentations at major oncology conferences from March 8, 2016, to the end of 2023. Publications were searched using the keywords "PD-1 and PD-L1, immune checkpoint inhibitor (ICI), and NSCLC". Subsequently, the publications selected focused on the effects of immunochemotherapy in NSCLC, and studies with less relevant to the therapeutic effects of immunotherapy were excluded. Eventually, a total of 46 publications were reviewed in the current assay.

Long-term survival data associated with immunochemotherapy

Before immunotherapy, advanced NSCLC patients with negative driver genes had a poor prognosis with a 5-year overall survival (OS) rate of less than 5%. The second-line and post-line treatment of immune monotherapy increased the 5-year OS rate to about 13–16% (3-5), the 5-year OS rate of first-line monotherapy was 31.9% and 16.6% in patients with high PD-L1 expression and PD-L1 positive, respectively (6,7). Therefore, whether immunochemotherapy can lead to better long-term survival and potential benefits to the entire population is of significant clinical concern.

Achieving long-term survival in the entire population

Two studies, KEYNOTE-407/189, were the first to demonstrate long-term survival data for immunochemotherapy. The median follow-up of 56.9 and 64.6 months, and the 5-year OS rate in patients with advanced squamous cell carcinoma and non-squamous cell NSCLC was 18.4% and 19.4%, respectively (8,9). In patients with non-squamous NSCLC, the 5-year OS rate of PD-L1 ≥50%, 1–49%, and <1% in the immunochemotherapy group were 29.6%, 19.8%, and 9.6%, respectively; in patients with squamous cell carcinoma, the 5-year OS rate of PD-L1 ≥50%, 1–49%, and <1% in the immunochemotherapy group was 23.3%, 20.6%, and 10.7%, respectively. Regardless of patients' pathological type and PD-L1 expression status, immunochemotherapy led to long-term survival, i.e., nearly 20% of patients with advanced carcinoma were cured, which is clinically significant.

Exploring the duration of immunotherapy that is associated with long-term survival

In clinics, the maximum duration of first-line immunotherapy is 35 cycles (about 2 years). However, in KEYNOTE-189 and KEYNOTE-407 studies, the 5-year OS rate of patients with non-squamous and squamous cell carcinoma, with a complete treatment of 2 years, was 71.9% and 69.5%, respectively (8,9), indicating that the patients that underwent 2 years of immunotherapy exhibited long-term survival. Therefore, it is essential to understand if administering immunotherapy for more than 2 years could lead to a more prolonged survival. A retrospective study reported at the American Society of

Clinical Oncology (ASCO) meeting showed that the patients with advanced NSCLC were divided into two groups based on the duration of first-line immunotherapy, with one group of patients (n=113) receiving immunotherapy for 2 years (range, 700–759 days) and the other group (n=593) receiving immunotherapy for more than 2 years (≥760 days). The results showed that the 4-year OS rate of the two groups was 79% and 81%, respectively, which was not significantly different between the two groups, suggesting that prolonged immunotherapy did not exhibit any additional survival benefits (10). The KEYNOTE-189/407 study evaluated the efficacy after redosing pembrolizumab monotherapy in patients who had completed 2 years of immunotherapy. The median time to initiate pembrolizumab restart therapy was 5.4 months (range, 0.9–18.2 months). The results showed a disease control rate (DCR) of 50% and progression-free survival (PFS) of 7.7 months after reusing pembrolizumab monotherapy, suggesting that patients who completed 2 years of treatment could benefit after restarting immunotherapy even if disease progression occurred later (11).

Application of immunochemotherapy in special populations

The first-line treatment of immunochemotherapy improved the survival of advanced NSCLC in the entire population; however, there are some challenges regarding the application of immunochemotherapy in special populations. For example, in a population with brain metastases and an elderly and oligometastatic population, the benefit of immunochemotherapy and an optimized treatment mode need to be explored.

Brain metastases

Patients with brain metastases are considered a major challenge in treating lung cancer, with a lack of effective therapeutic drugs and a poor prognosis. Immunotherapy has been explored in a population with brain metastases. A retrospective pooled analysis of three KEYNOTE-021/189/407 studies showed that pembrolizumab combined with chemotherapy significantly prolonged OS and reduced the risk of death by 52% compared to patients treated with chemotherapy alone in previously treated or untreated patients with stable brain metastases (12). ATEZO-BRAIN is a prospective, single-arm phase II study that evaluated the efficacy and safety of atezolizumab combined chemotherapy in NSCLC patients with brain metastases, and the median number of enrolled patients with brain metastases was five. The results showed that the overall objective response rate (ORR) was 45%, intracranial ORR was 42.5%, systemic PFS was 8.9 months, intracranial PFS was 6.9 months, and the 2-year OS rate reached 27.5% (13). At ASCO, a single-arm, multicenter phase II study reported the use of tislelizumab with pemetrexed and carboplatin in non-squamous NSCLC patients with untreated asymptomatic or stable brain metastases after radiotherapy. The results showed that the systemic ORR was 50.0%, the intracranial ORR was 56.7%, the median systemic PFS was 7.5 months, and the 1-year PFS rate was 36.8%, while the median intracranial PFS could not be achieved, and the 1-year intracranial PFS rate was 56.6% (14). These findings suggested that immunochemotherapy is an effective treatment strategy for treating patients with brain metastases and consistent intracranial and extracranial responses.

PD-L1 positive patients (≥75 years old)

Elderly patients account for many lung cancer patients, and several studies have shown that old age is not a contraindication for immunotherapy. However, no consistent conclusion exists on which immunotherapy strategy can be used for elderly patients. The Food and Drug Administration (FDA) pooled analysis results showed that there was no significant difference in OS between the immunochemotherapy and immune monotherapy group in a population with high PD-L1 expression, but the immune monotherapy regimen may exhibit better PFS and OS results in the elderly patients (≥75 years old) (15). This year's ASCO meeting reported the data from a multicentered real-world study evaluating the efficacy and safety of first-line immunochemotherapy in elderly patients (≥75 years old). This study included 1,245 patients with a median age of 78 years who received immunochemotherapy, immune monotherapy, platinum-based doublet chemotherapy, and monotherapy, with a median OS of 20.0, 19.8, 12.8, and 9.5 months, respectively. The patients in the immunochemotherapy and immune monotherapy groups were matched with propensity scores. The results showed that in patients with PD-L1 ≥1%, regardless of the expression status of PD-L1 (1–49% or ≥50%), there were no significant differences in the PFS and OS between the two groups; however, the incidence of grade ≥3 immune-related adverse event (irAE) in the immunochemotherapy group was significantly higher than

that in the immune monotherapy group (16). Therefore, for the elderly population (≥75 years old) and PD-L1 ≥1%, immune monotherapy seems to be a more suitable treatment strategy.

Oligometastatic populations

Oligometastasis is a specific diseased state of advanced NSCLC. The European Society for Radiotherapy and Oncology (ESTRO) and the European Organization for Research on Treatment of Cancer classified oligometastasis into new (first diagnosis of oligometastasis), repeated (diagnosis of new oligometastasis after treating oligometastasis), and induced oligometastasis (diagnosis of oligometastasis after treating multiple metastases). Previous prospective studies confirmed that radiotherapy after first-line systemic chemotherapy or targeted therapy improved the survival of oligometastatic patients; however, the data after first-line immunotherapy, chemotherapy, and radiotherapy for oligometastatic NSCLC are still limited. A retrospective study divided patients with advanced NSCLC who received first-line immunochemotherapy into two groups with or without radiotherapy to evaluate the efficacy and safety of first-line immunotherapy, chemotherapy, and radiotherapy group and the immunotherapy and chemotherapy group. The results suggested that the immunotherapy, chemotherapy, and radiotherapy group significantly improved PFS and OS (17). The first guidelines for local management of oligometastatic NSCLC were published by the American Society of Radiotherapy & Oncology and ESTRO. For patients with synchronous oligometastasis, three months of systemic therapy is recommended to evaluate the efficacy and tolerability of systemic therapy, followed by local therapy. However, it is essential to understand when to stop systemic therapy or to proceed simultaneously needs to be discussed by a multidisciplinary team, considering the long half-life of immunotherapy. It is not essential to continue immunotherapy with radiotherapy, but this requires a multidisciplinary team to guide treatment decisions for oligometastatic lung cancer.

Exploration of immunochemotherapy in driver gene mutation populations

Immunotherapy has revolutionized the changes for advanced NSCLC patients with negative driver genes, whereas the driver gene-positive population has a unique tumor immune microenvironment (TIME). Furthermore, whether immunotherapy can be a clinical treatment option for NSCLC patients with driver gene-positive remains controversial. Several immunochemotherapy studies have explored different treatment options for treating driver gene-positive patients.

EGFR mutation targeting drug-resistant population

Drug resistance in epidermal growth factor receptor (*EGFR*) mutation patients after tyrosine kinase inhibitor (TKI) treatment is inevitable, and immunotherapy can benefit EGFR-TKI-resistant patients must be further confirmed. Several studies demonstrated that the expression levels of PD-L1, the value of tumor mutation burden, and the level of tumor-infiltrating lymphocytes (TILs) in EGFR mutation patients were low, suggesting that patients with EGFR mutation were not the dominant population for immunotherapy, and the associated benefits are minimal (18,19). In several single-arm phase II studies, toripalimab combined chemotherapy, tislelizumab combined chemotherapy, and pembrolizumab combined chemotherapy exhibited good initial efficacy in EGFR-TKI-resistant populations. However, phase III studies are required for confirmation (20-22).

Recently, two global phase III studies of immunochemotherapy for EGFR-TKI-resistant populations have been published. In the CheckMate-722 study, nivolumab combined with chemotherapy did not significantly improve the median PFS in EGFR-TKI-resistant advanced NSCLC patients compared to chemotherapy alone (23). Similarly, the KEYNOTE-789 study published at this year's ASCO meeting showed that in advanced non-squamous NSCLC patients with EGFR-TKI resistance, pembrolizumab combined with chemotherapy did not prolong the patients' PFS and OS compared to the placebo combined with chemotherapy group (24). The application of immunochemotherapy in EGFR-TKI-resistant population is controversial and needs further exploration. A subgroup analysis of EGFR mutations was performed in an IMpower150 study, including patients with 123 EGFR mutations (91 EGFR-sensitive mutations) in an intention-to-treat population (n=1,202), of which 78 EGFR-sensitive mutations were previously treated with TKI [22 in the bevacizumab combined with atezolizumab and chemotherapy group (ABCP group), 28 in the bevacizumab combined with chemotherapy group (BCP group), and 28 in the atezolizumab combined with and chemotherapy group

(ACP group)]. The results showed that ABCP treatment group prolonged the OS compared to BCP treatment group in EGFR-sensitive mutation TKI-resistant population [27.8 *vs.* 18.1 months, hazard ratio (HR) 0.74] (25). This was the first time the four-drug combination strategy demonstrated survival benefits in EGFR-TKI-resistant populations, suggesting an immunomodulatory role of anti-angiogenic drugs in the tumor microenvironment. The ORIENT-31 study, a multicenter randomized controlled phase III study, confirmed that compared to the standard chemotherapy group (n=151), sintilimab combined with bevacizumab and chemotherapy group (n=148) significantly improved the ORR (43.9% *vs.* 25.3%) and PFS (6.9 *vs.* 4.3 months, HR 0.464) of EGFR-TKI-resistant population (26,27). In May this year, the National Medical Products Administration approved sintilimab combined with bevacizumab, pemetrexed, and cisplatin for treating EGFR-TKI-resistant patients with advanced NSCLC, bringing a new treatment option for EGFR-TKI-resistant patients. Therefore, for EGFR-TKI-resistant patients, including anti-angiogenesis drugs based on immunotherapy with chemotherapy may be a more suitable treatment plan.

ALK gene fusion in TKI-resistant population

There is little clinical evidence of immunotherapy for patients resistant to *ALK* fusion targeted therapy, and the effects of ALK-TKI therapy on the TIME were unclear. One study analyzed the samples from eight ALK-positive lung adenocarcinoma patients before and after targeted therapy by whole exome sequencing (WES) and RNA-seq. The results showed that the tumor neoantigen and mutation burden were significantly reduced after ALK-TKI treatment, suggesting that ALK-TKI treatment reduced the immunogenicity of tumors (28). Several small sample studies showed that immune monotherapy does not benefit patients with ALK fusion targeted resistance (29-31). Regarding immunochemotherapy, a phase II study evaluated the efficacy of pembrolizumab combined with chemotherapy in NSCLC patients with EGFR or ALK-positive targeted resistance. Seven patients with ALK-TKI resistance were included in the study, the ORR of immunochemotherapy was 28.6%, and the median PFS was only 2.9 months (22). The results suggested that ALK-TKI-resistant patients still have limited benefits from immunochemotherapy. At present, the research data of immunotherapy in the ALK-positive population are all small samples, and it still needs to be further explored in phase III studies with large samples in the future.

Population with rare driving gene mutations

In recent years, several infrequent target drugs have been approved for marketing. However, due to the accessibility of infrequent target drugs, whether first-line immunochemotherapy can bring additional survival benefits to patients with infrequent mutations in the initial treatment population is still lacking in prospective randomized controlled trials. In several previous phase III studies of immunochemotherapy, the patients with EGFR and ALK mutations were excluded. However, other populations with infrequent mutations were not excluded, so infrequent target mutations are not an "exempt population" for immunochemotherapy. At the previous year's ASCO meeting, FDA conducted a summary analysis of 12 randomized controlled trials submitted for market approval. The results showed that first-line immunochemotherapy OS benefits were consistent for Kirsten rat sarcoma viral oncogene (*KRAS*) mutation and KRAS wild-type patients, suggesting that first-line immunochemotherapy is suitable for patients with KRAS mutation (32). Immunotherapy data are mainly obtained from small sample retrospective studies for patients with other infrequent target mutations. Some studies have shown that immunotherapy may benefit patients with human epidermal growth factor receptor 2 (*HER-2*), B-Raf proto-oncogene, serine/threonine kinase (*BRAF*), and mesenchymal-to-epithelial transition exon 14 skipping mutations. However, due to the significant heterogeneity of the included population concerning the number of previous treatments and immunotherapy regimens, more evidence-based medical evidence remains to be confirmed in the future.

Optimization of the subsequent treatment strategy after assessing the progress of first-line immunochemotherapy

The median PFS for advanced NSCLC receiving first-line immunochemotherapy was 7–11 months, and most patients developed disease progression after first-line immunochemotherapy. Docetaxel ± antiangiogenic therapy is the current standard second-line treatment strategy, but its efficacy is not satisfactory. Several studies have explored the treatment mode after immunotherapy and chemotherapy disease progression to develop new treatment strategies.

Different treatment strategies were adopted as per the progression pattern of first-line immunotherapy

The pattern of progression after immunotherapy is divided into tumor oligoprogression and systemic progression, and local treatment may benefit patients with oligoprogression. In a study with 1,201 NSCLC patients who received immunotherapy from the Memorial Sloan Kettering Cancer Center (MSKCC), 56% of the secondary resistance population was dominated by oligo-progression, and local or surgical therapy exhibited better OS benefits than systemic therapy (33). In another retrospective study from China that included 500 NSCLC patients who received immunotherapy, the proportion of oligoprogression was 36.2%, suggesting that for patients with repetitive oligoprogression (oligoprogression with a history of oligometastasis), ablative therapy exhibits PFS and OS advantages (34). In addition, there was a retrospective study conducted in China indicated that immunotherapy beyond progression (IBP) was also beneficial for patients with advanced NSCLC who experienced progressive disease (PD) after receiving mono-immunotherapy or immunochemotherapy (35). Therefore, local treatment for patients with oligoprogression can lead to better survival benefits, while for patients with systemic progression, further exploration of more effective immunochemotherapy strategies is required.

Cross-line application of immune drugs and exploration of optimized immunochemotherapy strategies

Immunotherapy combined with anti-angiogenesis therapy demonstrated a synergistic mechanism. Anti-angiogenesis therapy improved the tumor microenvironment and reversed the drug resistance associated with immunotherapy. Several studies explored the efficacy of immunotherapy and anti-angiogenesis therapy in patients with progression of immunochemotherapy. Cabozantinib combined with atezolizumab showed an initial efficacy in the phase II study (36), and the phase III study results of the CONTACT-01 study were reported at the European Lung Cancer Congress (ELCC) meeting. This study evaluated the efficacy of atezolizumab combined with cabozantinib *vs.* docetaxel in advanced NSCLC patients treated with immune and platinum-containing chemotherapy (37). However, the study did not reach the primary endpoint, and there was no significant difference in OS between the combination and docetaxel groups. The analysis based on the duration of previous immunotherapy showed that patients treated for <6 months exhibited no OS benefit, while patients treated for ≥6 months of immunotherapy exhibited significant benefits. The results from another phase II lung-MAP substudy, S1800A, showed that in patients who showed previously failed chemotherapy with a PD-1/PD-L1 inhibitor combined with a platinum-containing regimen, ramucirumab combined with pembrolizumab group significantly improved the median OS compared to the standard regimen. Notably, patients enrolled in this study required a duration of prior immunotherapy of ≥84 days, and 69% of these patients had a duration of prior immunotherapy of ≥6 months (38). These two studies suggested that immunotherapy combined with anti-angiogenesis therapy may be suitable for those with a longer duration of first-line immunotherapy, and further studies are required for verification.

New immune target drugs and immunotherapy are another research hotspot. Soluble LAG-3 protein (eftilagimod alpha) can activate antigen-presenting cells and promote the proliferation of activated T cells (39), overcoming the drug resistance associated with immunotherapy. A phase II TACTI-002 study was reported at the 2023 ELCC meeting, evaluating eftilagimod alpha and pembrolizumab in the second-line treatment of metastatic NSCLC patients who were immune-resistant (67% immunochemotherapy-resistant). The results showed that the ORR was 8.3%, the DCR was 33%, the median OS was 9.9 months, and the 21-month OS rate was 39% (40). Compared to the historical data, the efficacy of combination therapy is better than that of single-agent docetaxel (21-month OS rate is 10–15%), and this treatment mode needs to be verified in phase III clinical trials. Furthermore, sleeve lobectomy for advanced NSCLC following neoadjuvant immunochemotherapy was confirmed to be feasible in a retrospective study conducted from 2016 to 2019 (41), which indicated surgical intervention may also be one of the effective treatments after receiving immunochemotherapy. In addition, there are still some novel combination treatment strategies in the early stage of clinical research exploration, such as immune combined with vaccine therapy, immune combined with TIL therapy, immune combined with intestinal flora transplantation therapy, immune combined with epigenetic therapy, which may provide more treatment options for patients resistant to immune combined with chemotherapy in the future.

Different drug resistance mechanisms and novel immune strategies

The drug resistance mechanisms associated with immunotherapy are complex and involve different immune, metabolic, and epigenetic mechanisms and their effects on microbial flora. There needs to be more clinical studies on precise population selection based on biomarkers or specific drug resistance mechanisms. HUDSON (phase II, multi-arm, and umbrella study) was a preliminary exploration of biomarker matching for patients with immunochemotherapy resistance, and combined treatment strategies were adopted according to different biomarkers (42). The results suggested that immunotherapy combined with ataxia telangiectasia and Rad3-related (ATR) inhibitor ceralasertib group showed preliminary efficacy, and it was still essential to explore the precise immune combination therapy strategy. According to different tumor immune subtypes, exploring reasonable combination treatment strategies may be the future research directive to overcome drug resistance.

Exploration of biomarkers for immunochemotherapy

The dominant population for immunochemotherapy is still unclear, and exploring appropriate biomarkers can maximize the clinical benefits associated with immunotherapy. The predictive value of tumor cell PD-L1 in immune combination therapy is limited, and the predictive efficacy of tumor mutation burden in different studies is inconsistent. Finding more effective biomarkers to screen the population that benefits from immunochemotherapy is essential.

Classification of TIME

TIME factors are closely related to the efficacy associated with immunotherapy. Kim *et al.* divided tumors into four types: PD-L1–/TIL– (type I), PD-L1+/TIL+ (type II), PD-L1–/TIL+ (type III), and PD-L1+/TIL– (type IV) based on the expression of PD-L1 in tumor cells and TILs (43). Type II tumors are more sensitive to immunotherapy, which needs to be confirmed by the data obtained from clinical studies. ORIENT-11 is a phase III study evaluating the efficacy and safety of sintilimab or placebo combined with first-line chemotherapy in advanced NSCLC. This study applied RNA sequencing and immunohistochemical (IHC) data in biomarker exploration, compared to the benefit of immunochemotherapy and chemotherapy alone in each of the four TIME classifications, and evaluated the relationship between the TIME classification model and the survival benefit of immunochemotherapy. The results showed that in the immunochemotherapy group, the patients with type II exhibited longer PFS and OS, PFS of the other three subtypes were similar, and the median OS of patients with type III and type IV was slightly longer than that of type I, while in the chemotherapy group, there was no significant difference in PFS and OS of each subtype (44). The research results showed that the TIME of tumor classification model helped achieve precision immunotherapy in advanced lung cancer, worthy of further exploration in future research.

Genomic characterization of tumors

Several studies demonstrated that genetic changes in tumors affect the efficacy of immunotherapy. The CHOICE-01 study evaluated the efficacy and safety of toripalimab or placebo combined with first-line chemotherapy against advanced NSCLC. The results of an exploratory biomarker analysis of the CHOICE-01 study prospectively used WES to explore biomarkers for immunotherapy at the genomic level. Compared with panel detection, WES achieved higher-depth sequencing to understand broader genome-level variation information and deeply analyze the correlation between genomic changes and the efficacy of immunochemotherapy. The results showed that in the toripalimab combined with chemotherapy group, patients with focal adhesion (FA)-PI3K-Akt signaling pathway and IL-7 signaling pathway gene mutations demonstrated longer PFS and OS, and patients with Switch (SWI)/sucrose non-fermenting (SNF) pathway gene mutation exhibited significant PFS benefit after immunochemotherapy (45,46). These findings suggested that genomic information of tumors may bring potential predictive value for immunochemotherapy and provide more accurate treatment strategies for clinical practice.

Circulating tumor DNA (ctDNA) clearance after immunotherapy

Liquid biomarkers have the advantages of non-invasive and dynamic monitoring. It represents the overall state of the tumor, which has been the hot spot for biomarker exploration in recent years. The ASCO meeting [2023] reported the results of liquid biomarker exploration in

the CHOICE-01 study, which analyzed the relationship between blood ctDNA clearance and the efficacy of immunochemotherapy by detecting dynamic changes in the blood ctDNA from C1D1 to C3D1. Through experimental results, it was demonstrated that the ctDNA clearance rate of toripalimab combined with chemotherapy group was higher than that of the placebo combined with chemotherapy group. The patients with ctDNA clearance at C3D1 exhibited significant OS benefits after immunochemotherapy, suggesting that the clearance of blood ctDNA after treatment can be used as a potential predictor of survival benefit after combined therapy (46). RATIONALE-304 and RATIONALE-307 studies at the 2023 American Association for Cancer Research (AACR) meeting reported the relationship between dynamic ctDNA levels and clinical treatment outcomes in advanced NSCLC patients treated with tislelizumab combined with chemotherapy during first-line treatment. This study analyzed paired ctDNA at and after baseline [first response (FR) or PD] to assess the impact of baseline and primary responses on the ctDNA levels of PFS and OS in both studies. The results showed that the changes in ctDNA levels from baseline to primary response were correlated with patients' clinical responses, and ctDNA analysis showed that significant decreases in ctDNA levels from baseline to primary response were correlated with better PFS and OS, further suggesting that ctDNA may be a biomarker of immunotherapy efficacy in advanced NSCLC patients (47). In the future, further prospective studies are required to further evaluate the value of ctDNA as a predictive biomarker for immunochemotherapy in NSCLC patients.

Multidimensional exploration of biomarkers to achieve precision immunotherapy

Several biomarkers have been used to predict the efficacy of immunotherapy, and it is of significant clinical value for establishing a prediction model composed of multiple biomarkers. Blood, tumor tissues, and feces of patients were collected before and during treatment, and biomarkers for predicting immune efficacy were analyzed in depth, dynamically monitored, and regulated. In the future, artificial intelligence technology will be used to integrate the multidimensional data of tumor biomarkers, such as DNA genomics, RNA transcriptome, proteomics, epigenetics, immunomics, and microbiome, and explore the prediction model of immunotherapy biomarkers, achieving precision immunotherapy (48).

Conclusions

Immunochemotherapy has ushered in a new era of advanced NSCLC, achieving long-term survival in a population with negative driver genes. Furthermore, its application in special populations has refined immune combination therapy. Immunochemotherapy showed intracranial and extracranial benefits in patients with brain metastases, especially in the elderly who were PD-L1 positive. Immune monotherapy might be a better treatment strategy, especially in the oligometastatic population, wherein including radiotherapy can improve the survival status of patients based on immunization and chemotherapy. Exploring immunochemotherapy in patients with driver gene mutations is still controversial. In the EGFR-positive TKI-resistant population, immunochemotherapy must be explored, and the four-drug strategy of immunization combined with bevacizumab and chemotherapy may be a more suitable treatment option. There is still a long way to go for immunotherapy in ALK-positive patients. In contrast, patients with KRAS mutation may be the dominant population for immunotherapy, and first-line immunochemotherapy can lead to increased survival. Overall, different immunochemotherapy strategies must be adopted according to the patients with different disease conditions in order to attempt to enhance treatment efficacy and improve survival rates. Meanwhile, according to the progression pattern of immunotherapy, further exploration is warranted regarding diverse coping strategies following disease progression subsequent to immunochemotherapy, in order to optimize treatment outcomes for such patients. Immunotherapy combined with anti-vascular therapy and immunotherapy combined with new target drugs must be further explored, and treatment strategies based on drug resistance mechanisms could be potential treatment options for the patients. Furthermore, the exploration of biomarkers in immunochemotherapy is crucial for enhancing clinical treatment efficacy, making it a prominent area of research. Leveraging artificial intelligence technology to integrate multi-omics data from tumor biomarkers and identify easily accessible biomarkers will significantly contribute to achieving accurate immune combination therapy. In the future, an in-depth exploration of multiple aspects of immunochemotherapy in advanced NSCLC will help NSCLC become a controllable chronic disease.

Acknowledgments

Funding: This article was funded by the Department of Science and Technology of Jilin Province (No. 20220203150SF), the Development and Reform Commission of Jilin Province (No. 2021C042-7 and No. 2021C043-1), and the National Cancer Center (No. NCC201907B01).

Footnote

Peer Review File: Available at https://cco.amegroups.com/article/view/10.21037/cco-23-92/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-23-92/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Wang T, Zhang L, Cheng Y. Clinical status and perspective on the application of immunotherapy combined with chemotherapy in advanced non-small cell lung cancer: a review. Chin Clin Oncol 2024;13(2):26. doi: 10.21037/cco-23-92