タイトル	155th Regular Meeting of the Medical Society of Toho University Professor Special Lecture Immune Checkpoint Inhibitors for Advanced Non-Small-Cell Lung Cancer
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公開者	The Medical Society of Toho University
発行日	2020.12.01
ISSN	21891990
掲載情報	Toho Journal of Medicine. 6(4). p.137-142.
資料種別	学術雑誌論文
内容記述	Review Article
著者版フラグ	publisher
JaLCDOI	info:doi/10.14994/tohojmed.2020-008
メタデータのＵＲＬ	https://mylibrary.toho-u.ac.jp/webopac/TD10670445

Professor Special Lecture: 155th Regular Meeting of the Medical Society of Toho University

Review Article

Immune Checkpoint Inhibitors for Advanced Non-Small-Cell Lung Cancer

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ABSTRACT: Unfortunately, lung cancer remains the leading cause of mortality in Japan. Until recently, the 5-year survival rate for patients with advanced non-small-cell lung cancer (NSCLC) was less than 5%. Since the recent introduction of inhibitors of programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1), systemic therapy for advanced, or metastatic NSCLC underwent a significant change. This review evaluates emerging data on the efficacy and safety of immunotherapy for advanced NSCLC. PD-1 immune checkpoint inhibitor monotherapy using nivolumab or pembrolizumab showed an impressive 5-year survival rate of around 15% in previously treated patients with advanced NSCLC. Next, the immune-related adverse events can occur, but severe toxicities, such as pneumonitis or colitis, are infrequent. Immunotherapy is now the standard first-line treatment of choice, applied as either monotherapy, or combined with chemotherapy. For patients with a PD-L1 tumor proportion score (TPS) ≧50%, single-agent pembrolizumab demonstrated improved overall survival (OS) in comparison with platinum-based chemotherapy in patients with both non-squamous and squamous NSCLC without driver mutations. First-line pembrolizumab, carboplatin or cisplatin plus pemetrexed, atezolizumab, bevacizumab, carboplatin plus paclitaxel, atezolizumab, and carboplatin plus nab-paclitaxel showed significantly improved OS, compared with platinum-based chemotherapy alone in patients with advanced non-squamous NSCLC regardless of PD-L1 expression. Among these combination treatments, the use of atezolizumab, bevacizumab, and carboplatin plus paclitaxel in patients with *EGFR* mutations and *ALK* gene rearrangements is encouraging and requires further exploration. Pembrolizumab and carboplatin plus nab-paclitaxel improved OS compared with chemotherapy in patients with squamous NSCLC. To select the most appropriate candidate for immunotherapy, the identification of accurate predictive biomarkers beyond PD-L1 expression remains essential. In addition, to increase the long-term survival rate, efforts to develop strategies to overcome immunotherapy resistance should be initiated.

Toho J Med 6 (4): 137–142, 2020

KEYWORDS: immunotherapy, lung cancer, programmed death-1, programmed death ligand-1

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DOI: 10.14994/tohojmed.2020-008

Received Apr. 14, 2020
Toho Journal of Medicine 6 (4), Dec. 1, 2020
ISSN 2189–1990, CODEN: TJMOA2

Introduction

Lung cancer is the leading cause of cancer-related mortality in Japan, and this disease accounted for 74,328 deaths in 2018. Non-small cell lung cancer (NSCLC) represents approximately 85% of lung cancers, and over half of patients with lung cancer present with metastatic disease at the time of initial presentation. For the last three decades, first-line systemic therapy for most patients with advanced or metastatic NSCLC consisted of platinum-based chemotherapy, which yields a 5-year survival rate less than 5%. Beyond cytotoxic chemotherapy, several targeted therapies were developed to address molecular addiction in the subset of tumors harboring actionable alterations, including inhibitors of the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), Braf (BRAF), and neurotrophic tropomyosin receptor kinase. These targeted therapies demonstrated substantially improved outcomes; however, the development of resistance is inevitable. In this landscape, the recent development of monoclonal antibodies targeting programmed death-1 (PD-1) or its ligand programmed death ligand-1 (PD-L1) revolutionized the treatment for patients with advanced NSCLC, particularly in patients without a targetable oncogene. Now, two PD-1 immune checkpoint inhibitors, nivolumab and pembrolizumab, and one PD-L1 immune checkpoint inhibitor, atezolizumab, are available for the treatment of metastatic NSCLC in Japan. Immunotherapy offers the potential for long-term survival benefit in a portion of patients with advanced NSCLC. In this review, the current status of immunotherapy for advanced NSCLC is discussed.

Immunotherapy Directed at PD-1

PD-1 is a transmembrane receptor that is expressed primarily on the surface of activated T cells. Its ligand, PD-L1, is expressed on tumor cells and infiltrating immune cells, and this interaction leads to T-cell inactivation. Malignancies can overexpress PD-L1 as a mechanism of defense against the host's immune system, and this interaction can be blocked with antibodies directed against PD-1 or its ligand. This strategy was proven to be an effective therapeutic option for many malignancies, including NSCLC. One of the most attractive features of PD-1/PD-L1 immune checkpoint inhibitors is that a subset of patients seems to demonstrate durable benefits.

Biomarkers can aid in identifying patients who are more likely to respond to single-agent immune checkpoint inhibitors. Clinical trials of antibodies targeting the PD-1 and PD-L1 pathway demonstrated that the PD-L1 tumor proportion score (TPS) measured by the PD-L1 immunohistochemical assay can identify patients more likely to respond to immune checkpoint inhibitors. Therefore, testing for PD-L1 should be performed in all patients with advanced NSCLC.

CheckMate 003, a dose-escalation phase I study of the anti-PD-1 antibody nivolumab in patients with solid tumors, registered the longest reported follow-up for survival in patients with NSCLC who were treated with immunotherapy after disease progression on other therapies. The estimated 5-year overall survival (OS) rate was 16%, for all treated patients (N = 129).[1] Keynote 001 is a phase I study to evaluate the side effects generated by, as well as the safety and antitumor activity of, pembrolizumab, the anti-PD-1 antibody, in patients with advanced NSCLC. 101 treatment-naïve and 449 previously treated patients are present in this study. The estimated 5-year OS was 23.2% for treatment-naïve patients and 15.5% for previously treated patients.[2] In patients with a PD-L1 TPS of 50% or greater, the 5-year OS was 29.6% and 25.0% in treatment-naïve and previously treated patients, respectively. Treatment with PD-1 antibody monotherapy provides durable antitumor activity and high 5-year OS rates in patients with advanced NSCLC.

Immunotherapy for NSCLC as Second-Line Treatment

CheckMate 017,[3] CheckMate 057,[4] Keynote-010,[5] and OAK[6] were phase III studies evaluating anti-PD-1 and anti-PD-L1 antibodies in patients with previously treated advanced NSCLC. These studies exhibited similar designs comparing PD-1/PD-L1 immune checkpoint inhibitors and docetaxel (standard of care) as second-line therapy among patients with advanced NSCLC, and all these studies showed that PD-1/PD-L1 immune checkpoint inhibitors improved OS with less severe toxicity. Next, PD-1/PD-L1 immune checkpoint inhibitors caused immune-related adverse events such as thyroids, pneumonitis, and colitis, and these events were often mild in severity, although serious toxicities can occur. Management of the immune-related adverse events includes discontinuation of therapy and administration of corticosteroids, which typically lead to improvement in symptoms. According to these results, single-agent PD-1/

Table 1 First-line Therapy for Advanced Non-Small-Cell-Lung Cancer (NSCLC) without Driver Mutations

Histological type	PD-L1 status	Treatment regimens
Squamous and non-squamous	PD-L1 ≧50%	Pembrolizumab
Non-squamous	any PD-L1	Pembrolizumab, carboplatin or cisplatin, and pemetrexed Atezolizumab, bevacizumab, carboplatin, and paclitaxel Atezolizumab, carboplatin, and nab-paclitaxel
Squamous	any PD-L1	Pembrolizumab, carboplatin, and nab-paclitaxel

PD-L1: programmed death ligand-1

PD-L1 immune checkpoint inhibitors, including nivolumab, pembrolizumab, or atezolizumab, can serve as the standard treatment modality for immunotherapy-naïve patients with advanced NSCLC in the second-line setting.

Immunotherapy Monotherapy for NSCLC as First-Line Treatment

Following the approval of PD-1/PD-L1 immune checkpoint inhibitors for use after initial treatment with platinum-based chemotherapy, clinical studies evaluating immune checkpoint inhibitors in the first-line setting were initiated. A phase III clinical study, KEYNOTE-024, randomized 305 patients with NSCLC who exhibited PD-L1 expression of more than 50% of cells and did not demonstrate *EGFR* mutations and *ALK* gene rearrangements. These patients received pembrolizumab or platinum-based chemotherapy.[7] Treatment with pembrolizumab increased the objective response rate (45% vs 28%), progression-free survival (median, 10.3 vs 6 months; HR, 0.50 [95% CI, 0.37-0.68]; $P<.001$), and OS (median, 30.0 vs 14.2 months; HR, 0.63 [95% CI, 0.47-0.86], $P=.002$). A lower frequency of severe adverse events results from pembrolizumab treatment (27% vs 53% of patients who exhibited grade ≧ 3 treatment-related adverse events). As a result, pembrolizumab monotherapy became the standard first-line treatment for patients with advanced NSCLC, in whom PD-L1 expression was seen in 50% or greater of their tumor cells (Table 1).

Combination Chemoimmunotherapy for NSCLC as First-Line Treatment

Platinum-based chemotherapy has long been a standard of care in lung cancer. At present, the combination of a platinum doublet and immune checkpoint inhibitor was proven to augment the efficacy of treatment compared with chemotherapy alone for patients with advanced NSCLC with both non-squamous and squamous histologic findings, irrespective of PD-L1 expression (Table 1). Certain lines of evidence suggest that the antitumor effect of chemotherapy is mediated through both a cytotoxic effect and immunological effects, including reducing the regulatory T-cell effect and enhancing the cross-presentation of tumor antigens.[8] Researchers found that chemotherapy induces changes in PD-L1 TPS, providing additional support for combining chemotherapy and PD-1/PD-L1 immune checkpoint inhibitors.[9]

KEYNOTE-189[10] was a phase III study (N = 616) of platinum-based chemotherapy (pemetrexed plus cisplatin or carboplatin) with or without pembrolizumab for patients with non-squamous NSCLC without *EGFR* mutations and *ALK* gene rearrangements. The combination of chemotherapy and pembrolizumab showed an improved response rate vs chemotherapy alone (48% vs 19%; $P<.001$), progression-free survival (median, 8.8 months vs 4.9 months; HR, 0.52 [95% CI, 0.43-0.64]; $P<.001$), and OS rate (HR, 0.49 [95% CI, 0.38-0.64]; $P<.001$). Also, benefits occurred regardless of PD-L1 TPS.

Similar results were seen in the phase III KEYNOTE-407 study (N = 559), which enrolled patients with squamous NSCLC.[11] Patients were randomized to pembrolizumab, carboplatin plus either paclitaxel or nab-paclitaxel, or chemotherapy alone. Patients in the pembrolizumab combination arm demonstrated significantly improved OS (median, 15.9 months vs 11.3 months; HR, 0.54 [95% CI, 0.49-0.85]; $P=.001$), compared with chemotherapy alone.

Atezolizumab, an anti-PD-L1 antibody, also demonstrated beneficial outcomes in combination with chemotherapy as a first-line treatment option. The phase III IMpower 150 trial randomized PD-L1 unselected patients with stage IV or recurrent metastatic non-squamous NSCLC. The patient's received the control arm of carboplatin, paclitaxel, and bevacizumab (triplet therapy); or

carboplatin, paclitaxel, and atezolizumab; or carboplatin, paclitaxel, bevacizumab, and atezolizumab (quadruplet therapy).[12] The study used a hierarchical analysis, and the initial report compared the quadruplet therapy with the control arm of triplet therapy (N = 692). Patients receiving quadruplet therapy demonstrated improved progression-free survival vs patients receiving triplet therapy (median, 8.3 months vs 6.8 months; HR, 0.62 [95% CI, 0.52-0.74; $P<.001$]) as well as improved OS (median, 19.2 months vs 14.7 months; HR, 0.78 [95% CI, 0.64-0.96]; $P=.02$). The benefits of progression-free survival were irrespective of TPS. Interestingly, this study enrolled a subset of patients with *EGFR* and *ALK* abnormalities into a subgroup analysis, and these patients seemed to be conferred a similar benefit compared with patients with wild-type *EGFR* and *ALK* NSCLC, although the number of such patients was small. To confirm the efficacy of quadruplet therapy for patients with driver mutations, prospective trials in this population are needed.

IMpower 130 is a phase III study that evaluates atezolizumab plus carboplatin and nab-paclitaxel vs carboplatin and nab-paclitaxel for PD-L1-unselected patients with stage IV non-squamous NSCLC in the first-line setting.[13] Atezolizumab and chemotherapy arm showed improved progression-free survival (median, 7.0 vs 5.5 months; HR, 0.64 [95% CI, 0.54-0.77]; P<.0001) and OS (median, 18.6 vs 13.9 months; HR, 0.79; [95% CI, 0.64-0.98]; P=.033), compared with chemotherapy alone.

According to the results of such large-scale randomized studies, the incorporation of immunotherapy into the first-line setting for all patients, except those with molecular alterations who respond to targeted therapy, is recommended. Next, for patients without these molecular alterations, PD-L1 testing determines available treatment options. Patients with good performance status with PD-L1 TPS of less than 50% receive combination chemoimmunotherapy. For patients with a TPS of 50% or greater, the standard treatment modality would include either pembrolizumab monotherapy or immunochemotherapy.

Conclusion

The use of PD-1/PD-L1 immune checkpoint inhibitors significantly changed the treatment regimen of patients with advanced or metastatic NSCLC. At present, immunotherapy is employed as the standard first-line treatment as either monotherapy or combined with chemotherapy. These advances are substantial; however, long-term durable responses are seen in only a limited number of patients. Next, novel biomarkers to predict the efficacy of combined chemotherapy and immunotherapy need to be characterized. Additionally, as an increasing number of patients are treated with immunotherapy, progression would be seen following the response. Hence, to develop strategies to overcome therapy resistance, further efforts should be initiated.

Conflicts of interest: Kazuma Kishi reports grants from Chugai Pharmaceutical Company Limited, grants from Nippon Boehringer Ingelheim Company Limited, and research funds from Taiho Pharmaceutical Company Limited, outside the submitted work.

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