Lung Cancer Immunotherapy

Subjects: Allergy

Contributor: Tomomari Kinoshita

Lung cancer is one of the most deadly of solid cancers. Advanced lung cancer is a prevalent disease with high mortality and low response to conventional cytotoxic therapies. Lung cancer is classified into different histological types, such as adenocarcinoma, squamous cell carcinoma, large cell carcinoma (commonly referred to as non-small cell lung cancer (NSCLC)), and small cell lung cancer (SCLC), and the treatment strategy varies depending on the histological type, as well as the degree of progression.

lung cancer immunotherapy immune checkpoint inhibitor

1. Introduction

Lung cancer is one of the most deadly of solid cancers [1]. Advanced lung cancer is a prevalent disease with high mortality and low response to conventional cytotoxic therapies. Lung cancer is classified into different histological types, such as adenocarcinoma, squamous cell carcinoma, large cell carcinoma (commonly referred to as non-small cell lung cancer (NSCLC)), and small cell lung cancer (SCLC), and the treatment strategy varies depending on the histological type, as well as the degree of progression. The recommended medical management for most patients with advanced stage NSCLC, mainly chemotherapy, improved progression-free survival (PFS) of 4–6 months and overall survival (OS) of about 12–18 months [2][3]. PFS and OS have been marginally improved by newer agents such as angiogenesis inhibitors, such as bevacizumab [4] and targeted chemotherapy based on oncogenic mutations [5]. Recently, immunotherapeutic agents targeting immune checkpoint pathways have shown great promise in clinical trials and are rapidly being incorporated into the standard of care for advanced stage NSCLC.

2. Rise of Immune Checkpoint Inhibitors in Lung Cancer Treatment

Immune checkpoints are proteins on the surface of T-cells and other immune cells that function as negative regulators of immune activation by a variety of antigens, including tumor antigens. ICIs are a class of immunotherapeutic agents that harness the intrinsic immune response to tumor antigens by removing the brakes on T-cell activation by antigen-presenting cells (APCs). The first checkpoint discovered was cytotoxic T-lymphocyte antigen-4 (CTLA-4), and ipilimumab, an ICI developed to target CTLA-4, has shown prolonged survival in melanoma [6]. Such ICI-mediated activation of anti-tumor activity has shown great promise in other tumor types as well. For example, treatment with ICIs targeting CTLA-4 or another immune checkpoint, programmed cell death 1

(PD-1), has been shown to be effective in advanced melanoma [7][8], colon cancer with mismatch-repair deficiency [9], Hodgkin lymphoma [10], and renal cell carcinoma [11].

Among the various checkpoint pathways, the PD-1 pathway, consisting of the receptor (PD-1) and its reciprocal ligands (programmed death-ligand 1/2 (PD-L1 and PD-L2, respectively)), CTLA-4 pathway, have been most intensely studied in NSCLC in recent years. Monoclonal antibodies targeting PD-1 (e.g., nivolumab, pembrolizumab, sintilimab, cemiplimab), PD-L1 (e.g., atezolizumab, durvalumab), or CTLA-4 (ipilimumab), have been investigated in clinical trials for lung cancer and have demonstrated significant improvements in survival.

2.1. Nivolumab

Clinically, nivolumab showed an OS advantage over docetaxel, the conventional standard of chemotherapy in 2015. Of note, there is the tail plateau effect seen in nivolumab-treated patients, in which the OS and PFS curves almost cease to decline after a certain point, indicating a long-term progression-free survival effect that was thought to be impossible to achieve with conventional therapy (CheckMate 017, 057) [12][13]. The phase III Checkmate 816 trial is currently underway and is attempting to compare nivolumab plus two platinums with chemotherapy as neoadjuvant therapy for resectable NSCLC (stage IB-IIIA).

2.2. Pembrolizumab

Pembrolizumab is the most widely used ICI in lung cancer currently. KEYNOTE-010 trial showed the efficacy of pembrolizumab for patients with previously treated, PD-L1-positive, advanced NSCLC [14]. Furthermore, the efficacy of single-agent pembrolizumab as a first-line treatment for NSCLC with high PD-L1 expression was demonstrated (KEYNOTE-024) [15][16]. OS improvement after pembrolizumab alone treatment was investigated in patients with PD-L1 of 1% or higher to reconfirm its efficacy (KEYNOTE-042) [17]. Another comparative phase III study of platinum-based pemetrexed plus pembrolizumab in chemotherapy-naive advanced non-squamous NSCLC without EGFR or ALK mutations showed prolonged OS regardless of PD-L1 expression status (KEYNOTE-189) [18]. For squamous cell carcinoma, a comparative phase III study of platinum plus paclitaxel plus pembrolizumab showed an add-on effect both on OS and PFS (KEYNOTE-407) [19].

2.3. Sintilimab

A randomized, double-blind, phase III trial of sintilimab (fully human anti-PD-1 antibody) with pemetrexed and platinum was conducted in China. In Chinese patients with previously untreated locally advanced or metastatic non-squamous NSCLC, the addition of sintilimab to pemetrexed and platinum-based chemotherapy significantly prolonged PFS with a manageable safety profile compared to chemotherapy alone (ORIENT-11) [20]. In the second report of this study, it was shown that high expression of major histocompatibility complex (MHC) class II, as well as high immune cell infiltration could be predictive biomarkers in this sintilimab trial [21].

2.4. Cemiplimab

In the first-line treatment of advanced NSCLC with PD-L1 expression rates of 50% or higher, cemiplimab monotherapy significantly improves OS and PFS compared with chemotherapy. As well as sintilimab, cemiplimab may provide a new treatment option for patients with high PD-L1-expressing NSCLC.

2.5. Atezolizumab

The IMPower110 trial showed that atezolizumab alone significantly prolonged OS compared to platinum-based chemotherapy in patients with NSCLC of any histology with high expression of PD-L1 [22]. In 2019, IMPower130 study, which was designed to evaluate the efficacy and safety of the combination of atezolizumab and chemotherapy (carboplatin and nab-paclitaxel) versus chemotherapy alone as first-line therapy for non-squamous NSCLC, showed survival improvement of OS and PFS [23]. On the other hand, atezolizumab to platinum (carboplatin or cisplatin) plus pemetrexed in chemotherapy-naive patients with advanced non-squamous or NSCLC showed an add-on effect not on OS but on PFS in the phase III study in 2020 (IMPower132) [24]. In the first-line treatment of stage IV squamous NSCLC, the addition of atezolizumab to platinum-based chemotherapy significantly improved PFS, but not OS (IMPower131) [25].

The combination of atezolizumab with paclitaxel plus bevacizumab in chemotherapy-naive patients with metastatic non-squamous NSCLC patients showed its additional affect in IMPower150 study [26][27]. However, in the final analyses of IMPower150, the additional effect of atezolizumab resulted in a numeric, but not statistically significant, improvement in OS. This may be correlated with PD-L1 expression on tumor cells [28].

Atezolizumab was shown to be effective and safe as neoadjuvant immunotherapy for stage IB-IIIB resectable NSCLC in the phase II trial (LCMC3) [29]. In addition, many clinical trials are currently underway for preoperative therapy using ICIs (NCT02818920, NCT03425643, NCT02259621, NCT03081689, NCT02998528, NCT03158129, NCT03456063, NCT02927301). Moreover, for SCLC, the IMpower133 study, which aimed to evaluate the add-on effect of atezolizumab to carboplatin plus etoposide in chemotherapy-naïve SCLC patients, showed a significant improvement in OS (median OS was 12.3 with atezolizumab and 10.3 months with placebo). This was very sensational news in the treatment of SCLC, which has remained unchanged from the current standard of care for over 20 years. It is clinically meaningful and will be a new standard treatment option [30].

2.6. Durvalumab

A phase III study comparing durvalumab and placebo in patients with non-resectable, locally advanced NSCLC who were progression-free after concurrent chemoradiation showed significant improvement in OS and PFS [31][32].

2.7. Ipilimumab

Based on the results of CheckMate 227, nivolumab plus ipilimumab is recommended as first-line therapy for NSCLC with metastatic disease, regardless of PD-L1 expression, although the amount of tumor mutation burden (TMB) may be related [33] (discussed below). Additionally, it was investigated whether the addition of two cycles of chemotherapy to this combination would further enhance the clinical benefit. The combination of nivolumab and

ipilimumab plus two cycles of chemotherapy resulted in a significant improvement in overall survival and a favorable risk-benefit profile compared with chemotherapy alone (Checkmate 9LA) [34]. In addition, as mentioned above, the efficacy of single-agent pembrolizumab as first-line therapy for NSCLC with high PD-L1 expression has been demonstrated [15][16], however, the KEYNOTE-598 trial, which aimed to show an add-on effect of ipilimumab to pembrolizumab, failed to demonstrate such an effect and was terminated [35]. A phase III study of the add-on effect of ipilimumab to platinum plus etoposide in SCLC also failed to show OS benefit [36].

3. Future Prospects of Lung Cancer Immunotherapy

An interesting, and potentially very attractive, new approach is to take a personalized approach to immunotherapy by harnessing the power of genetic sequencing. Although it is well known that cigarette smoking is associated with lung cancer carcinogenesis, there are many non-synonymous mutations in smoking-related lung cancers that have a molecular smoking signature [37], and can generate tumor-specific MHC class I restriction epitopes. Thus, every tumor is highly specific and has a unique antigen profile. This so-called tumor mutanome can be revealed by deep sequencing, and the immunogenicity of mutated peptides can be predicted in silico. These peptides can be used to track tumor-specific T-cell responses and can be incorporated into personalized vaccines [38][39]. Peptide neoantigen vaccines may not be sufficient to induce an effective tumor-specific immune response, and a combination therapy approach (e.g., ICI) may be required [40][41].

Successful immunotherapy of lung cancer requires a better understanding of immune escape and immunosuppression in lung cancer, and learning how to monitor immunity, edit immunity, and reactivate immunity in cancer. By learning to understand cancer immunosurveillance, immunoediting, and how to reactivate cancer immunity, we can embark on a future full of possibilities to use immunotherapy as a reliable lung cancer treatment. The logical combination of nivolumab and ipilimumab in melanoma and NSCLC looks promising, although there are considerable side effects [42]. Several studies have examined the efficacy of nivolumab in combination with various anticancer agents, including chemotherapy, molecular-target therapy, bevacizumab, and other immunotherapies [43]. T-cell immunoreceptor with Ig and ITIM domains (TIGIT) potently inhibits innate and adaptive immunity through a variety of mechanisms [44]. Blocking both TIGIT and PD-1/PD-L1 pathways enhances the expansion and function of tumor antigen-specific $CD8^+$ T-cells [45][46]. In a phase I study of vibostolimab (an anti-TIGIT antibody) in patients with advanced NSCLC after ICI treatment, this treatment was well tolerated as monotherapy and showed moderate anti-tumor activity. A randomized phase II trial of tiragolumab, another anti-TIGIT antibody, in combination with atezolizumab showed a modest but significant improvement in PFS versus placebo plus atezolizumab (CITYSCAPE) [47]. Preliminary data from a clinical trial of LAG-3 antibody (liratrimab) in combination with nivolumab in melanoma patients suggested that it was more effective than nivolumab alone, suggesting that the anti-LAG-3 antibody may have clinical efficacy as a third ICI pathway following PD-1 and CTLA-4 [47]. There are also many clinical trials running to explore the efficacy of ICI as preoperative adjuvant therapies for lung cancer [29][48][49]. Epigenetic therapies can also be used to induce tumors to be more responsive to immunotherapy [50]. The long-term efficacy of ICIs is still unknown, and clinicians face the problems of how to

identify patients for treatment such as biomarker issue and how to manage the toxicity that occurs and the cost of these therapies.

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