

Lung Adenocarcinoma treatment: Traditional therapy and Immunotherapy

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Abstract. The previous years, the incidence of lung adenocarcinoma (LADC) has gradually increased. As a subset of non-small cell lung cancer (NSCLC), LADC is very severe (12% 5-year survival rate) and often occurs in people who have never smoked. With forward genetic research, scientists have found a series of related mutant genes. Among them, EGFR is the most common gene mutation in Asian LADC. This article systematically summarizes and analyzes the existing treatment methods and related clinical data for EGFR mutations in LADC and puts forward the prospect of feasible treatment methods in the future. This includes traditional chemotherapy and radiotherapy, targeted drug therapy (fifth generation and FDA-approved drugs), and immunotherapies.

Keywords: Lung adenocarcinoma, Traditional therapy, Target Drugs, Immunotherapy

1. Introduction

Lung adenocarcinoma (LADC) belonging to the subtype of NSCLC is one of the majority lung cancers [1]. The data shows around 40% of lung cancers are LADC [1]. Although lung cancers are strongly associated with smoking, LADC is commonly diagnosed in non-smoking people [1]. This is because LADC relates to many gene mutations, such as the oncogenic alterations in KRAS, EGFR, ALK, ERBB2, BRAF, PIK3CA, NRAS, CTNNB1, and the tumor suppressor alterations in TP53, STK11, CDKN2A, NF1 [2]. According to the patient's symptoms, There are five stages of LADC (Stage 0, I, II, III, and IV), with stage III marking the beginning of lymph node metastasis and stage IV marking the beginning of distant metastases [1]. With only a 12% overall 5-year survival rate, LADC is a relatively fatal disease [1].

For now, there are several treatments for LADC, they can be divided into two main categories: traditional therapy and immunotherapy. In traditional therapy, radiotherapy is only restricted to patients who are not suitable for surgery, and chemotherapy's toxic effects are relatively high [3]. Thus, a more promising and now widely used approach is targeted drug therapy. The clinical trials revealed that the Tyrosine kinase (TK) inhibitors (TKIs) shows a great success in the treatment of LADC patients caused by EGFR mutations and ALK fusions [4]. Recently, the fourth generation of EGFR-targeted medicine has been approved by FDA for treatment [5]. However, the developed drug resistance in the later treatment also makes the treatment to be less effective.

To overcome that, scientists have been investigating some new approaches by using immunotherapy. Two immune checkpoint inhibitors (ICIs), CTLA4 and PD-1 inhibitors, have been shown to be very effective in treating advanced LADC [3]. In addition, the adoptive immunotherapy that uses the chimeric antigen receptor (CAR) directed T cells to target the EGFR-mutated cells also achieves a better response [3].

Although LADC is deadly, its future treatments are promising. Currently, there are several ongoing clinical trials that try to improve both efficiency and efficacy. For example, the combinational therapy combined the two ICIs, the adjuvant addition that tries to reduce the target drug resistance, and the improvement of CAR T cells therapy. This paper reviews both the traditional treatments and the immunotherapy approaches of LADC and points out some prospective improvements.

2. Traditional treatment

2.1. Chemotherapy & Radiotherapy

Regarding traditional therapy, the most common and well-known one is chemotherapy. However, the side effects that are carried out by chemotherapy are inescapable. For example, cisplatin-based chemotherapy will induce peripheral neuropathy due to its toxicity [6]. Notably, according to the research, the severeness of chemotherapy is highly dependent on the patients' performance status [6]. Patients with a good performance status are more likely to benefit from the treatment. The other type of traditional therapy is radiotherapy, which most commonly is external-beam radiation therapy [7]. Compared to chemotherapy, radiotherapy is only restricted to patients who are not suitable for the surgery. However, due to its ability to kill stem cells, it can result in lots of complications and side effects. One expected side effect is radiation-induced esophagitis, which is an acute toxicity effect [8]. The symptoms of radiation-induced esophagitis include nausea, dysphagia, odynophagia, and so on [8]. Patients may even experience dehydration and malnutrition if the symptoms are much more severe [8]. Thus, although radiotherapy is effective, it is also toxic.

2.2. Target drugs

To reduce the toxicity and increase the effectiveness, scientists now have developed the target drug therapy. LADC, as introduced previously is usually induced by the mutation in the tumor's oncogene. There are several genes that have the capability to trigger LADC, this paper mainly focuses on the treatment of EGFR mutation, which is also the most frequent mutation gene of LADC in Asian people [4]. EGFR with the full name epidermal growth factor, is a receptor involved in a signal pathway [3]. When it binds to its ligand (EGF or TGF- α), the receptor will then undergo auto-phosphorylation through homo-dimerization or hetero-dimerization [3]. The EGFR mutation linked to LADC is found to be either in exon 19 (deletion) or in L858R (point mutation), which are all present in the TK domain and near the ATP cleft [3]. If the mutation presents, EGFR will undergo auto-phosphorylation without a ligand binding and sequentially trigger the three subsequent signal pathways (the RAS/RAF/MAPK pathway, the PI3K/AKT pathway, the JAK/STAT pathway) [3].

With the mechanism being understood, scientists developed several TK inhibitors to treat LADC patients. For now, there are five FDA-approved generations of TKI. The first generation of EGFR TKIs function by attaching to ATP-binding regions, which blocks the activation of the downstream signal [9]. The three FDA-approved drugs are Gefitinib, Erlotinib, and Icotinib [9]. However, the findings show that chemotherapy patients do not differ significantly in progression-free survival (PFS) or overall survival (OS) [9]. The second generation of EGFR TKIs works through irreversible binding to the active ErbB receptor family members, which blocks its enzymatic activity [9]. The two FDA-approved drugs are Afatinib and Dacomitinib. The second generation somewhat overcomes drug resistance compared to the previous generation [9]. The clinical trial also revealed that patients' PFS increased apparently compared to the chemotherapy groups [9].

However, although some approved EGFR TKIs can improve PFS and overall response rate (ORR), they all inevitably developed the drugs resistance [9]. Several different mechanisms, including as the EGFR T790M alteration, CMET duplication, HER2 overexpression, histological shift to small-cell histology, and some others, can contribute to this acquired treatment resistance [9]. Of these, the most popular (49% ~ 63%) one is T790M mutation, which significantly reduced the binding affinity of the first and second generation of drugs [9]. Thus, the next (3rd) generation of EGFR TKIs is published to solve that problem. Working through covalently binding to the T790M, the third generation EGFR TKIs can inhibit the positive drug resistance and sensitivity [9]. The FDA-approved drugs are Osimertinib (taggriso, AZD9291), Rocicetinib (CO1686), Olmutinib (HM61713), and AC0010 [9]. According to a global clinical trial (AURA) on Osimertinib, the phase I (AURA 1) data shows that the ORR is high with 61% in T790M positive patients and 21% in T790M negative patients [9]. AURA 2 shows the final ORR is approximately 71% and AURA 3 reveals a significantly recreated mPFS [9]. Additionally, up to 97% of diseases are controlled [9].

In contrast with the third generation, the fourth generation EGFR TKIs target a different drug resistance mutation, C797S [9]. The occurrence of EGFR C797S is about 32% [9]. The first FDA-approved fourth-generation drug is EAI045, which can target both T790M and C797S [9]. However, according to the research, it only works when used with the combination of cetuximab [9]. It works by preventing the cells from hiding the L858R or T790M mutation, and when combined with cetuximab it can prevent EGF binding to EGFR [9]. Currently, the drug is still under the preclinical phase, so more research data is needed to increase the convince.

Although the emerging third generation and fourth generation of drugs have brought a lot of hope to patients with LADC, there are still many blockades to be overcome. First, all the published drugs have adverse events, in which patients may experience diarrhea, rash, nausea, decreased appetite, and so on. Moreover, the acquired drug resistance is also an ongoing problem. New mutations will keep presenting along with the treatment process. For example, C797S is not the only resistance mutation toward the third generation EGFR TKIs. In that case, instead of merely focusing on the conventional therapy and target therapy, researchers recently have been seeking some new approaches to treat LADC, such as combinational therapy that combined TKIs with chemotherapy, combined TKIs with anti-angiogenic drugs, and immunotherapy.

3. Immunotherapy

The most widely used immunotherapy methods are ICI, which mainly are CTLA4 inhibitors and PD-1 inhibitors. Their work mechanisms are quite similar, which all work through downregulating the immune response. It is conventionally known that the T cell activation needs some co-stimulatory signals except for the TCR-MHC interaction. The co-stimulatory signals can however be inhibitory or stimulatory. Only when the net signals are stimulatory, T cells can start to proliferate and generate the immune response. Usually, the B7 molecules expressed by the antigen-presenting cell (APC) will attach to the CD28 molecules (on T cells), which will then lead to the T cell activation [10].

3.1. CTLA4 ICI

CTLA4 is a molecule homologous to the CD28, but it will generate an inhibitory signal when binding to B7 [10]. Also, compared with CD28, CTLA4 has a higher binding affinity toward B7 [10]. Moreover, the binding of CD28 with B7 will up-regulate the expression of CTLA4 [10]. Thus, when CTLA4 binds to B7, it will generate a net negative signal and prevent T cells from activating. In that case, the IL-2 production, T cell differentiation, and T cell survival will be reduced [10]. Likewise, the B7/CD28 family member, PD-1, can also inhibit T cells from activation [10]. Tumor cells, when present, will up-regulate PD-L1's expression, which subsequently bind to PD-1 to escape T cells' killing [10].

Based on that, scientists developed the ICIs, which are monoclonal antibodies that bind to the targets and prevent the generation of net negative signals. These antibodies can be divided into three groups: those that target CTLA4, those that target PD-1, and those that target PD-L1. FDA has approved several ICIs to treat LADC in the clinical trial.

For CTLA4, the FDA-approved drugs are ipilimumab and tremelimumab [11]. According to the phase III clinical trials data that treat the LADC patients combined with chemotherapy, the PFS is slightly improved (about 1 month) [11]. Also, the overall reaction is 32%, which is around 14% higher than the control group [11]. The phase III clinical trials that treat patients with ipilimumab alone are still ongoing, so more research data will be renewed [11].

3.2. PD-1 ICIs & PD-L1 ICIs

For PD-1 ICIs, FDA-approved drugs are Nivolumab and Pembrolizumab [11]. One phase III clinical data revealed that using Nivolumab alone in the treatment slightly improved PFS and ORR compared to chemotherapy [12]. However, Nivolumab is significantly lower in the incidence of high-grade adverse effects (17.6% compared to 50.6%) [12]. In contrast, Pembrolizumab's phase III

clinical trial shows that Pembrolizumab can increase the PFS, especially in patients who express a high level of PD-L1 [12]. The data also shows a high level of safety compared to chemotherapy [12].

For PD-L1, the FDA-approved drugs are Atezolizumab, Durvakumab, and Ascekumab [11]. However, all three drugs' effects are dependent on the patients' PD-L1 expression [12]. Only individuals with greater than 50% PD-L1 expression, the drug will start to show some effects in extending PFS [12]. The phase III clinical trials of these drugs are still ongoing.

Although the emerging ICIs gradually become the newest and most promising treatment for lung cancers, their adverse events are still not negligible. Due ICIs mechanism that works through activating T cells, it may lead to an over-reactive state in which the over-reactivated T cells will attack the normal tissue cells [13]. These toxic effects are so-called immune-related adverse events (irAEs) [13]. Patients in this state may experience nephritis, myositis, myocarditis, and so on [13]. If severe, patients will die of these adverse events.

3.3. CAR T-cells Therapy

Another under-investigated immunotherapy method is CAR-T cell therapy, which uses the edited T cell to treat the target tumor cells [14]. Recently, CAR has been reaching its fifth generation. As mentioned previously, there are several mutations can lead to LADC, which provide lots of targets for CAR T-cells. For instance, the MSLN-CAR, EGFR-CAR, MUCI-CAR, and so on [14]. According to a phase I/II clinical data that published in 2020, 5 of 11 patients that injected with EGFR-CAR T-cells stabilized for 8 months [14]. Nevertheless, further data is needed to be convinced.

Notably, the newly emerging immunotherapy advantages in long-term treatment compared to traditional therapy. It provides a way for the patients to escape from the unavoidable drug resistance. ICIs since their therapeutic effects were discovered, it has been becoming cutting-edge treatments. Scientists also point out that ICIs will revolute the treatment of lung cancers in the next few decades [11].

4. Future Improvements

A range of combination therapies has been investigated to overcome the encountered limitations and improve future treatment efficiency. The frontier research includes the biomarker-driven approaches, the TKI-ICI combined approaches, and the combined ICIs approaches. The biomarker approach is using the EGFR TKI combined with biomarkers that target the identified EGFR TKI resistance mechanism, to reduce the drug resistance [15]. The clinical data revealed that this approach can increase patients' ORR [15]. The TKI-ICI approach is combining the EGFR TKI with either the PD1/PD-L1 or CTLA4 inhibitors to increase treatment efficiency [16]. However, the clinical data related to this approach tends to be polarized. In some clinical data, patients' ORR increased significantly (even up to 75%) while in other clinical data, patients show almost no effects compared to the control group [16]. Lastly, combinational therapy that combines two ICIs (PD-1 with CTLA4 or PD-L1 with CTLA4) to treat the patients is also under trial [12]. Existing data, however, are insufficient to demonstrate its impact; more future data are required.

5. Conclusions

EGFR TKIs that function through precisely inactivate the downstream signal pathways is more effective and less harmful than traditional therapy. The third generation of drugs, such as Osimertinib, now have been prescribed to LADC patients worldwide and even used as a first-line treatment [9]. However, later in treatment, all drugs will inevitably experience resistance due to the drug resistance mutation. Although new generations of drugs continue to improve resistance to previous drugs, new resistance mutations are still emerging. It is worth mentioning that the overall benefit of the patient is far greater than the drug resistance, so EGFR TKIs are still one of the front-line treatments.

ICIs, such as PD1/PD-L1 and CTLA4, act by enhancing T-cell immunity and may transform future LADC therapy. Currently, clinical studies using ICIs as first-line therapy are ongoing. Available data suggest that they, especially PD-1, can prolong patients' PFS. Moreover, if the injection amount is well controlled, it generally does not cause strong toxic reactions. But the over-activation of the immune system due to injections still needs to be considered. Meanwhile, as an emerging immunotherapy, CAR T cell therapy's application in lung cancers still requires further research.

There are also other ongoing trials try to solve the blockades faced by the previously mentioned treatments. Combination therapy of different combinations is one of them. In a word, LADC has broad and promising therapeutic prospects, and the improvement of treatment will be an ongoing process.

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