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Current therapy of small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC)

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Abstract. In recent years, with the rapid development of molecular immunology and related biotechnology, immunotherapy has made breakthrough progress in tumor treatment. The main object of this paper is the current clinical treatment of different lung cancer and their advantages and disadvantages. Through the literature review method, the latest and most standard treatment methods were selected and summarized. Studies have found that chemotherapy, especially platinum-based chemotherapy, is still the most effective means for lung cancer in clinical practice, and immunotherapy mainly relies on combination with chemotherapy to play a role. However, as a new treatment method, epidemic therapy is becoming increasingly mature, and compared with traditional chemotherapy, it has greater research and development potential and broader prospects. The research and development of immunotherapy will be the focus of the therapies for lung cancer in the future. Researchers need to tailor treatment methods based on the principles of individualized treatment to optimize the design and outcomes of clinical studies.

Keywords: SCLC, NSCLC, current therapy.

1. Introduction

In general, lung cancer is a serious health threat to humans. Lung cancer, an important branch of cancer, is a high-risk cancer whose incidence rate ranks only second to breast cancer. Lung cancer can be classified into two Small Cell Lung Cancer (SCLC) and Non-small Cell Lung Cancer (NSCLC). SCLC, accounts for 20% of the lung cancer patients, develops and transfers in a fast pace; NSCLC, accounts for 80% lung cancer patients, develops and transfers at a corresponding slow pace, but has little symptom, so it's hard to be recognized in early stage. In the world, lung cancer is a major cancer morbidity and death causes in different regions and race. Especially in these developing countries, with the acceleration of industrialization, the incidence and fatality rate of lung cancer increase significantly. In 2019, more than 10 million people died from cancer, while lung cancers showed the highest death rate [1].

This article mainly focuses on the different therapies for lung cancer in order to predict the developing direction of lung cancer therapies. The following researches will carry out mainly by literature research methods and comparative and analytical methods. Through classifying lung cancer into two main kinds first, the article introduces the basic framework of lung cancer. Then, collects the information on latest lung cancer therapies by literature research methods. Finally, compares the

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survival rates of different treatments to find out the effective therapies for different lung cancers until now and make the rough forecast base on it. It has to say to be a rough prediction since the accuracy of reference will fade due to the daily update research progress, but in general, it may play a guiding role for future research in some extent.

2. SCLC

SCLC is a type of tumor with rapid proliferation, high malignancy, early widespread metastasis, and susceptibility to endocrine dysfunction syndrome. Most SCLC patients are diagnosed as extensive stage, difficult to cure, and have a poor prognosis.

2.1. First-line combination chemotherapy regimen

Lung cancer has a high sensitivity to chemotherapy in the early stages. Frontline standard chemotherapy has a high response rate for small cell lung cancer patients, so it can effectively control the condition at the beginning.

2.1.1. Irinotecan combined with cisplatin. Irinotecan is a broad-spectrum anti-tumor drug, which can prevent tumor cells from dividing by interfering with DNA replication of tumor cells. Static or proliferating tumor cells contain a large amount of DNA Topoisomerase I. Irinotecan, as a specific inhibitor of DNA Topoisomerase I, is metabolized to SN-38 by carboxylesterase in most tissues. Then, SN-38 binds to the DNA Topoisomerase I complex that specifically Sexual inhibition the DNA reconnection step, leading to DNA single strand breaks, thus blocking DNA replication bifurcations, leading to cytotoxicity. This cytotoxicity is time-dependent and S-phase specific, leading to irreversible DNA damage during the cell replication phase, ultimately leading to tumor cell death, thereby blocking the diffusion and growth of small cell lung cancer cells. Therefore, irinotecan can effectively kill stationary or proliferating tumor cells.

Cisplatin is a metal platinum type complex that is a cytotoxic cyclic non-specific anti-tumor drug. It has a strong anti-cancer effect and can combine with DNA, thus inhibiting cancer cells' DNA replication.

In addition to the common adverse effects of chemotherapy, such as bone marrow suppression, hepatorenal toxicity, neurotoxicity, gastrointestinal reactions, and alopecia, etc. The side effects of Irinotecan and cisplatin are mainly reflected in the digestive tract and their impact on renal function. During chemotherapy, complications such as nausea, vomiting, diarrhea, and renal dysfunction may occur.

2.1.2. Etoposide combined with cisplatin. Etoposide is a kind of xylan anti-tumor drug extracted from xylol, and its chemical formula is C29H32O13. It mainly acts on the S phase or G2 phase of tumor cell division and inhibits the aggregation and disintegration of microtubules by combining DNA Topoisomerase II and DNA to form stable reversible complex. This impedes the mitosis process and DNA repair of tumor cells. In addition, when combined with cisplatin, etoposide can enhance the anticancer effect of cisplatin.

Cisplatin plus etoposide chemotherapy usually causes digestive system dysfunction, nausea, vomiting, diarrhea, loss of appetite and other symptoms, some patients may also appear peripheral nerve damage, motor disorders, myalgia, upper and lower limb paresthesia and other symptoms, a few patients can also appear brain dysfunction. In addition, it may affect the blood system, resulting in leukopenia, thrombocytopenia and other myelosuppression.

2.1.3. Difference of etoposide with cisplatin (EP) and Irinotecan with cisplatin (IP): According to recent research analysis, compared to the EP regimen, the IP regimen significantly raised the 1 or 2-year survival rates of previously untreated SCLC patients [2]. However, no remarkable difference in objective response rate (ORR) and disease control rate (DCR) between the IP and EP regimens was shown [2]. Adverse symptoms in IP, such as grade 3/4 leukopenia and incidence of anemia was

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significantly lower than that in EP, but the adverse effect of grade 3/4 vomiting and diarrhea was greatly higher than that in the EP group [2]. Although the overall efficacy of Etoposide or irinotecan with platinum is similar, recent research shows that irinotecan plus platinum is more suitable for the therapy for local SCLC patients, and helps reduce the risk of the central nervous system [3]. Compared with EP, IP has less hematology toxicity [4].

Most patients receiving first-line chemotherapy relapse within 1-2 years. Once the disease relapses, the 5-year survival rate is quite low due to the patient's susceptibility to relapse or drug resistance, resulting in a poor prognosis. In addition, some patients may progress and fail in the short term [4]. At present, there are no relevant testing methods and methods that can predict the relevant situation of drug-resistant/refractory patients [5].

2.2. Second-line combination chemotherapy regimen

For patients with SCLC who have failed first-line chemotherapy, the current standard treatment method is to use topotecan plus cisplatin as second-line treatment. There is research that reports topotecan may have the ability to give patients better overall survival benefits and extend their lives compared to irinotecan, paclitaxel, and docetaxel.

Topotecan is a drug with anti-tumor activity that approved for usage in second-line treatment of SCLC [6]. It can inhibit the replication of rapidly dividing cells by the way that destroying the normal function of ribozyme Topoisomerase I. It can combine with the Topoisomerase I-DNA complex, block reconnection of the broken DNA single strands, and inhibit DNA repair, thus affecting DNA replication, thus affecting the proliferation of cancer cells.

Non-cumulative anemia, neutropenia, and thrombocytopenia are common adverse reactions. Besides, in patients treated with topotecan, the incidence of Grade 3/4 anemia is significant [6]. In patients with SCLC who received topotecan, majority of the non-hematology adverse events were Grade 1 or Grade 2. Gastrointestinal disorders, hair loss, and fatigue are also common [6].

The response rate to drugs is average, and further researches are needed to locate the use of topotecan in drugs used for the treatment of SCLC. In addition, its use has limitation for SCLC, and recurrent SCLC remains very challenging.

2.3. Immunotherapy

In SCLC, the response rate of first-line platinum chemotherapy is stable, but the response lacks persistence. Therefore, the survival rate of patients is not satisfactory. However, SCLC was invented for a long time after chemotherapy. There are almost no breakthrough treatment strategies and there is no improvement in patient prognosis. The introduction of immune checkpoint inhibitors (ICIs) (such as the PD-1, the PD-L10, etc.) has changed the treatment method and improved the survival rate of SCLC patients. In immunotherapy, commonly used drugs are clinically approved PD-1 and PDL-1 antibodies. The application of these drugs mainly focuses on advanced tumors and has a certain therapeutic effect on patients with chemotherapy resistance. In clinical practice, a combination of immunotherapy and chemotherapy is commonly used for treatment.

2.3.1. Atezolizumab. Atezolizumab is the first approved immune checkpoint inhibitor. In addition to requiring genetic mutations, cancer cells must also find a way to escape the immune system, otherwise they will be killed by immune cells. One strategy is to inhibit the T cell proliferation and production of cytokine by binding the PD-1 ligands to PD-1 receptors on the T cells, thereby inhibiting the monitoring of tumors by active immune T cells. Through this signaling pathway, the activity of immune cells is suppressed. Atezolizumab, a new drug called PD-1 inhibitor, disrupts the relationship between cancer cells and immune cells by disrupting the connection between PD-1 and L1, allowing immune cells to attack cancer. Atezolizumab combines with PD-L1 to block its interaction with PD-1 receptors and thus, activating anti-tumor immune responses, blocking PD-L1 activity, and leading to reduced tumor growth.

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According to the multi drug I/III IMpower133 trial, compared with the single drug carboplatin plus Etoposide, the induction treatment of atezolizumab combined with carboplatin plus Etoposide, and then the maintenance treatment of single drug atezolizumab significantly prolonged the total survival period (OS) and progression free survival period (PFS). Importantly, adding atezolizumab to chemotherapy can improve survival outcomes without affecting patients' health-related quality of life.

Grade 3-4 hematological adverse reactions, rash and hypothyroidism. In addition, some common side effects of atezolizumab use include fatigue, nausea, constipation, cough, Tachypnea, and loss of appetite. When used in combination with other drugs, it can cause more serious side effects.

2.3.2. Durvalumab. Durvalumab selectively blocks interaction between the PD-L1 and PD-1 to improve the anti-tumor immune response, increase the activation of T-cell. In a co transplanted human tumor and immune cell xenograft mouse model, Durvalumab blockade of PD-L1 is associated with a decrease in tumor size [7].

In the critical phase III CASPIAN trial of ES-SCLC patients, comparing with chemotherapy alone for up to 6 cycles, patients treated by using durvalumab plus chemotherapy for up to 4 cycles and later maintaining the usage of durvalumab, shows longer OS and favorable progression free survival risk ratio. Compared with the chemotherapy group alone, durvalumab and chemotherapy group has more patients with objective reactions. The efficacy was also maintained over the follow-up periods [7].

peripheral edema, fatigue, dermatitis, rash, pruritus, hyperglycemia, hypocalcemia, hyponatremia, hyperkalemia, hypothyroidism, constipation, decreased appetite, colitis, diarrhea, nausea, abdominal pain, lymphocytopenia, elevated serum ALT, hepatitis, infection, difficulty urinating, etc.

2.3.3. Nivolumab. Nivolumab is an antibody to human immunoglobulin G4 (gG4) that can combine with PD-1 and therefor blocks its interaction with PD-L1. It mediates immune responses through the PD-1 pathway, including anti-tumor immune responses, as a tumor suppressor factor that hinders tumor development.

According to a recent report, 61.5% patients experienced a sustained DOR of at least 1 year [10]. Overall, nivolumab monotherapy provides a long-lasting response and is well tolerated [8]. In addition, nivolumab can also improve the function of existing anti-tumor T cells.

Side effects of Nivolumab include fatigue, nausea, diarrhea, anorexia, rash, pruritus, Bone marrow suppression and neutropenia. As the drugs cause the patient's immunity to decline, it may cause lung and bronchitis, nerve injury, peripheral neuropathy, headache, dizziness and other symptoms. It may also lead to endocrine disorders, such as excessive or insufficient secretion of thyroid hormones.

2.3.4. Difference of atezolizumab, durvalumab and nivolumab. Compared to atezolizumab, durvalumab has a statistical advantage in ORR, and the risk of having adverse events about immune in durvalumab is significantly higher compared to atezolizumab [9]. The research results showed that no statistically big differences in PFS and OS between atezolizumab, durvalumab, and nivolumab was found [9]. Compared to the use of EP alone, the addition of EP with atezolizumab, durvalumab, and nivolumab has significant benefits in OS (HR of nivolumab=0.67, 95% CI=0.46-0.98, HR of Atezolizumab=0.70, 0.54-0.91, HR of Durvalumab =0.73, 0.59-0.90). During the experiment, nivolumab had the highest probability of ranking first in the treatment group [10]. Compared to using EP alone, the PFS of all EP+ICI combinations is longer, and nivolumab ranks first in PFS [9]. In addition, the probability of occurrence of level 3-4 adverse events with Nivolumab is the highest [10]. Among all combinations of ICIs and EP, the PFS and OS of nivolumab are the better, but in the network meta-analysis, nivolumab has the higher 3-4 adverse events [10].

As a newly developed therapy, the approvals of it differ between different countries. In addition, the development of predictive biomarkers for immunotherapy response to SCLC is still in its infancy. The specific treatment method and efficacy of this treatment also need to be further explored.

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3. NSCLC

NSCLC is a malignant lung tumor. Under the microscope, it appears as abnormal nucleus, large cells, and abundant cytoplasm. Compared with SCLC, its cancer cells grow and divide relatively slowly and spread and metastasize later.

3.1. Platinum-based first-line chemotherapy regimen

3.1.1. Platinum combined with paclitaxel. Taxol is a semi-synthetic paclitaxel anti-microtubule drug, which has a great antagonistic effect on the activity of cancer cells. Taxane in paclitaxel can destroy the balance between protein dimer and microtubule, gradually promote microtubule aggregation, affect the stability of Tubulin itself, control and reduce the number of free stomach proteins, inhibit the division and proliferation of cancer cells, so as to achieve a good anti-cancer effect and significantly inhibit the activity of cancer cells.

A recent report analyzed 52 patients evaluated 4 weeks after chemotherapy, including 6 complete remission (CR), 18 partial remission (PR), 19 unchanged (NC), and 9 progressive disease (PD) [13]. The total effective rate (CR+PR) was 46.2%, the median survival time was 38 weeks, and the one-year survival rate was 43%. The effective rate of paclitaxel plus cisplatin to treat advanced NSCLC is 36.5%. In addition, the literature mentions that the effective rate of paclitaxel plus carboplatin to treat advanced NSCLC patients is 46%. Platinum combined with paclitaxel is an effective method for treating NSCLC [11].

The most common symptoms are gastrointestinal symptoms, nausea, and vomiting. Then there is blood toxicity. Both paclitaxel and platinum have obvious Bone marrow suppression effects. Therefore, a decrease in blood cells is very common. In addition, paclitaxel can also cause hair loss and neurotoxicity. Other side effects, such as damage to liver and kidney function, are relatively rare. According to reports, among 52 patients, 24 cases (46.2%) had a decrease in white blood cells, including 9 cases (17.3%) with a decrease in white blood cells ranging from 3 to 4 degrees. 5 cases developed fever due to neutropenia and required antibiotics and G-CSF blood raising treatment [11]. Due to routine preventive anti vomiting treatment, only 6 patients (11.6%) experienced 1-2 degree nausea and vomiting. 21 cases (40.4%) had hair loss; Three patients can tolerate finger numbness. There were no liver or kidney damage, allergic reactions, or treatment-related deaths in the entire group [11].

3.1.2. Cisplatin combined with docetaxel. Docetaxel is an anti-tumor drug of paclitaxel, which can effectively combine with human Tubulin to gradually transform Tubulin into stable microtubules. By inhibiting the reticular structure of human microtubules, docetaxel can affect the generation of microtubules and the fixation function of microtubules, thus inhibiting Mitosis of human tumor cells, and ultimately achieving the goal of anti-tumor [12].

According to recent experimental reports, out of 53 patients, 10 cases (18.87%) achieved complete remission (after treatment, the tumor lesion basically disappeared, the symptoms and signs of lung cancer basically disappeared, and the duration was> 4 weeks); 13 cases (24.53%) showed partial remission (after treatment, the tumor lesion shrank by more than 50%, no new lesions appeared, the symptoms and signs of lung cancer improved significantly, and the duration was> 4 weeks); 20 cases (37.74%) were stable (after treatment, the tumor lesion decreased by no more than 50% or increased by no more than 25%, no new lesions appeared, and the symptoms and signs of lung cancer improved to some extent, lasting for> 4 weeks); There were 10 cases of disease progression, accounting for 18.87% [14]. The overall clinical remission rate was 43.40%, and the disease control rate was 81.13%. Overall, cisplatin plus docetaxel to treat NSCLC has a good clinical effect and can effectively control the patient's condition [12].

The harm of paclitaxel drugs mainly lies in the damage to hair, hair roots, and hair follicles. After taking paclitaxel drugs, patients may experience severe hair loss. Docetaxel may cause pain in the muscles, bones, and joints throughout the body, as well as numbness and tingling of the surrounding

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nerves. Especially docetaxel may cause peripheral nerve poisoning caused by numbness in hands and feet. Other adverse reactions include leukopenia, neutropenia, thrombocytopenia, gastrointestinal reactions, liver and kidney dysfunction, and bone marrow suppression.

3.1.3. The difference of docetaxel and paclitaxel. From its pharmacological effects, it can be seen that although docetaxel belongs to paclitaxel, compared with paclitaxel, the anti-tumor drug has significantly lower toxicity, better efficacy, and more significant drug value [12]. According to reports, the total effective rates of each treatment group (docetaxel platinum (DP): 96.1%, paclitaxel platinum (PP): 94%, $p< 0.001$). The median time for PFS in patients receiving DP and PP treatment was 16 months and 15 months, respectively. The median OS time for DP and PP treatment was 19.2 months and 29.7 months, respectively. The incidence of nausea, vomiting, neuropathy, and allergic reactions is similar. The incidence of grade 1-2 mucositis or Esophagitis, anemia and pneumonia in PP group was higher. The incidence of adverse events and toxicity varies relying on which chemotherapy regimen is used [13].

3.2. Immunotherapy

Nivolumab is the PD-1 inhibitor while Ipilimumab is the CTLA-4 inhibitor. PD-1 inhibitors mainly act on the stage of T cell action, blocking the combination, restoring the T cells function to kill tumor cells, and inhibiting tumor growth. CTLA-4 inhibitors mainly act on the activation stage of T cells, bind to CTLA-4 on the initial T cell surface, promote T cell proliferation and activation, and mainly act on lymph nodes. These two drugs have different but complementary mechanisms of action.

After the 54.8 months follow-up, compared to chemotherapy, the duration of OS in patients with PD-L1($\geq$ 1%) (HR=0.76; 95%CI: 0.65-0.90) and PD-L1($<$ 1%) (0.64; 0.51-0.81) was longer; the 4-year OS rate of nivolumab combined with ipilimumab was 29% vs 18%; 24% vs 10%. Benefits were observed in the treatments [14].

Rash is common in immune mediated adverse events, which occurred within the 6 months and subsided within 3 months after the treatment, mainly systemic Corticosteroid [14].

4. Conclusion

In summary, chemotherapy is still the mainstream treatment for SCLC and NSCLC. However, due to the limited efficacy of chemotherapy for advanced lung cancer and the difficulty of making a major breakthrough at this stage, immunotherapy has replaced chemotherapy as a more promising treatment. At present, the research and development of immunotherapy mainly focuses on PD-1, PD-L1 and CTLA-4, and the therapeutic means used are mostly concentrated in combination with chemotherapy. As for the future development trend, the development of immunotherapy will be the main breakthrough in cancer treatment, and the research and development of lung cancer treatment will focus on immunotherapy. And in the future, immunotherapy will occupy a larger proportion in the cancer treatment.

References

[1] Lin L, Li Z, Yan L, Liu Y, Yang H, Li H. Global, regional, and national cancer incidence and death for 29 cancer groups in 2019 and trends analysis of the global cancer burden, 1990-2019. J Hematol Oncol. 2021 Nov 22;14(1):197.

[2] Fu J, Fang S, Wen Y, Wang Y, Yin X, Wang D. The efficacy and safety of irinotecan combined with nedaplatin in the treatment of small cell lung cancer. J BUON. 2020 Jul-Aug;25(4):1707-1713.

[3] Shang Nana. Clinical comparison of different first-line chemotherapy regimens in the treatment of brain metastases in small cell lung cancer [J]. Chinese medical engineering, 2021, 29(04):129-130.

[4] Pan D, Hou M, Li H, Yu P, Liu J. Irinotecan plus cisplatin compared with etoposide plus cisplatin for small cell lung cancer: a randomized clinical trial. Zhongguo Fei Ai Za Zhi. 2006 Oct 20;9(5):443-6. PMID: 21176468.

[5] CAI Kel, Xie Zhilong, Liu Yingao et al. Advances in molecular mechanisms of chemotherapy resistance in small cell lung cancer [J]. Hainan Medicine,2022,33(16):2145-2147.

[6] Ormrod D, Spencer CM. Topotecan: a review of its efficacy in small cell lung cancer. Drugs. 1999 Sep;58(3):533-51.

[7] Al-Salama ZT. Durvalumab: A Review in Extensive-Stage SCLC NCCCCC.Target Oncol. 2021 Nov;16(6):857-864. Epub 2021 Nov 3. Erratum in: Target Oncol. 2022 Jan;17(1):91.

[8] Ready N, Farago AF, de Braud F, Atmaca A, Hellmann MD, Schneider JG, Spigel DR, Moreno V, Chau I, Hann CL, Eder JP, Steele NL, Pieters A, Fairchild J, Antonia SJ. Third-Line Nivolumab Monotherapy in Recurrent SCLC: CheckMate 032. J Thorac Oncol. 2019 Feb;14(2):237-244. Epub 2018 Oct 10.

[9] Chen J, Wang J, Xu H. Comparison of atezolizumab, durvalumab, pembrolizumab, and nivolumab as first-line treatment in patients with extensive-stage small cell lung cancer: A systematic review and network meta-analysis. Medicine (Baltimore). 2021 Apr 16;100(15):e25180.

[10] Chen HL, Tu YK, Chang HM, Lee TH, Wu KL, Tsai YC, Lee MH, Yang CJ, Hung JY, Chong IW. Systematic Review and Network Meta-Analysis of Immune Checkpoint Inhibitors in Combination with Chemotherapy as a First-Line Therapy for Extensive-Stage Small Cell Carcinoma. Cancers (Basel). 2020 Dec 3;12(12):3629.

[11] Wang Huaqing, CUI Xiuzhen, ZHANG Wanling, LIU Xianming, ZHANG Huilai. Effect of paclitaxel and cisplatin in the treatment of advanced non-small cell lung cancer (a clinical report of 52 cases)[J]. Chinese Oncology Clinic,2001,(12):35-36+40.

[12] Lv L, Lv J. Clinical efficacy of cisplatin combined with docetaxel in the treatment of non-small cell lung cancer [J]. Journal of Clinical Rational Use of Medicine, 2019,15(04):107-110.

[13] Akdeniz N, Küçüköner M, Kaplan MA, Urakçı Z, Karhan O, Sezgin Y, Bilen E, Ebinç S, Teke F, Laçin Ş, Alan Ö, Ercelep Ö, Işıkdoğan A, Yumuk PF. Comparison of three different chemotherapy regimens for concomitant chemoradiotherapy in locally advanced non-small cell lung cancer. Int J Clin Oncol. 2020 Dec;25(12):2015-2024.

[14] Paz-Ares LG, Ramalingam SS, Ciuleanu TE, Lee JS, Urban L, Caro RB, Park K, Sakai H, Ohe Y, Nishio M, Audigier-Valette C, Burgers JA et.al First-Line Nivolumab Plus Ipilimumab in Advanced NSCLC: 4-Year Outcomes From the Randomized, Open-Label, Phase 3 CheckMate 227 Part 1 Trial. J Thorac Oncol. 2022 Feb;17(2):289-308. Epub 2021 Oct 12.