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Recent Development in NSCLC Immunotherapies: Mechanisms, Advantages and Research Findings

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Abstract. The NSCLC is a severe and common chronic disease in the whole world, and it has high mortality, which threatens human life. Therefore, the treatment of NSCLC is a hot topic in both society and the medical field. Nowadays, the treatment of NSCLC has many choices, for example, chemotherapeutic agents and radiotherapy drug treatments, these treatments of NSCLC are limited and have a lot of side effects to the patients, like unavoidable vomiting, hair loss, etc. The immunotherapist is the latest cancer treatment and it can improve curative effects and reduce adverse reactions. This article is based on the mechanism of NSCLC incidence and development and discusses the immunotherapies of NSCLC including the monoclonal antibody, immunity checkpoint inhibitors, and tumor therapeutic vaccines. It talks about the mechanisms of these treatments and the recent research findings of these treatments. It can provide references to the NSCLC clinical treatment and the clinical application of immunotherapies fields. This article also mentions the limitations and the challenges of tumor therapeutic vaccines, which can inspire researchers to find solutions and the progress of relevant limitations and challenges.

Keywords: NSCLC; clinical treatment; Immunotherapies.

1. Introdction

Nowadays, cancer is a severe and common chronic disease in the whole world, and it has high mortality, which threatens human life. Among many kinds of cancers, carcinoma of the lungs has extremely high incidence and mortality. According to the latest data collected, in 2022, the number of lung cancer cases reached 2,480,675 and it accounts for 12.4% of new cancer cases worldwide in 2022 [1]. In new lung cancer cases, the incidence of non-small cell lung cancer (NSCLC) reaches 82.1% [2]. Therefore, the treatment of NSCLC is a hot topic in the society and medical field.

NSCLC is a heterogeneous lesion at the molecular level. As same as the other kinds of cancer, the NSCLC is the variation of the gene in lung cells. The code change in the proto-oncogene and the tumor suppressor gene, and the expression level are changed by the gene variation. The expression of the proto-oncogene increases and the expression of the tumor suppressor gene decreases, which makes the cell clone abnormal. Meanwhile, the signaling molecules (like CD20, PD-L1, EGFR) in the cancer cell convey the message to mislead the body and systems. The immune system can't recognize and clean the tumor cells in time, which gives the tumors a chance to develop. Up to now, the methods to treat NSCLC have many choices, including resection, chemotherapeutic agents, and radiotherapy drug treatments. The resection is a physiological method to clean the boundary-clear tumor. The chemotherapeutic agent uses chemical drugs to inhibit tumor growth or clean the tumor, however, it also influences the healthy cells. Radiotherapy is a therapy using radiation with high energy to clean the tumor, but it will affect the other organs at the same time [3]. As previously described, these treatments for NSCLC are limited and have a lot of side effects on the patients, like unavoidable vomiting, hair loss, etc. Immunotherapy is the latest cancer treatment by uses biological agents to enhance the ability and sensitivity of immunocytes and the immune system to recognize tumor cells or to cooperate with the immune system to clean the tumor cells. This kind of treatment can improve curative effect and reduce side effects.

This article is about the immunotherapy of NSCLC. It will introduce the comparatively mature monoclonal antibody therapy and immune checkpoint inhibitor (ICI) therapy, and it will include the

combination therapy of the above two immunotherapies and the conventional therapies. It will also introduce the tumor therapeutic vaccine, which is in the developing period. This article aims to provide advice and references to the clinical treatment of NSCLS.

2. The Pathogenesis of NSCLC

2.1. The Etiology

The etiology of NSCLC is as same as the other kinds of cancer. The NSCLC is the gene variation happening in lung cells. The gene codes change on the proto-oncogene and the tumor suppressor gene, and the expression level of these genes is changed by the gene variation. The expression of the proto-oncogene decreases while the expression of the tumor suppressor gene decreases, which urges the cells to clone abnormally. Meanwhile, the surface of tumor cells forms some signaling molecules such as CD20, PD-L1, EGFR, etc. to mislead the body and the systems. The immune system can't recognize and clean the tumor cells in time, which gives the tumors a chance to develop. As time goes by, the tumor cells develop and change the environment by the autocrine and the porcine from the tumor cells, so that the microenvironment changes to be of advantage to the tumor development. For example, the tumor cells will secrete VEGF, PDGF, and the other signaling molecules to switch on the proliferation of EC and fibroblasts, smooth muscle cells to achieve tumor angiogenesis.

2.2. Common Pathogenic Factors

The factors of NSCLC are various. The most common factors like cigarettes, air pollution, and occupational exposure, for example, asbestos, silicon dioxide, dust, etc. [4] Meanwhile, the radiation and the chemical material also cause the NSCLC. Based on the data from WHO, smoking is the main cause of lung cancer, responsible for about 85% of all lung cancer cases [5]. Meanwhile, NSCLC is hard to find in the early stage, because the symptoms of lung cancer are similar to the common respiratory disease, therefore, the cancer cases are almost found in the later stage which has limited therapies that can be chosen.

2.3. Common Therapies of NSCLC

Up to now, the choices of NSCLC treatments are various. The conventional therapies to treat NSCLC are surgical resection, chemotherapy, radiotherapy, and target therapy. However, these therapies have their side effects and their limits. Surgical resection is an effective therapy but it can not clean diffuse NSCLC. The chemotherapy is to kill tumor cells by chemical drugs and it can also kill the common cells in the body and cause several side effects like hair loss, diarrhea, appetite loss, etc. Radiotherapy can use the high energy radio to clean the cancer cells, while it leads to the patients getting headaches and other serious side effects. Common therapies have their advantages and different levels of limits and side effects, therefore, scientists are still searching for more effective treatments with fewer side effects and limits.

3. Monoclonal Antibody (mAb)

3.1. Therapeutic Mechanisms and Preparation Process

3.1.1. Therapeutic Mechanisms

MAb is a biological agent that specifically binds the target molecules to inhibit tumor development or to promote tumor cells' switch-on apoptosis program. As a kind of antibody, the mAb is made up of two height chains and two light chains, forming a Y shape. The handle of Y is called a crystalline fragment (FC), and the two arms of Y are called antigen-binding fragments (Fab). The fragment of amino acid residues in Fab makes it easier to occur sequence changes than FC, therefore, Fab has the function of specific antigen recognition. In conclusion, Fab can specifically recognize the tumor-associated antigen and regulate downstream signaling, and FC has the function of recognizing and

binding the immunocytes that express the FC receptor and the alexin in blood to mediate the antibody or alexin-dependent cytotoxicity and the antibody-dependent phagocytosis.

3.1.2. Preparation Process

The preparation process of mAb has several steps, antigen preparation, animal immunization with antigen, the preparation of hybridoma cells with the splenic cells from immunized animals and the myeloma cells, the screening and cloning of the hybridoma cells, and mAb manufacture with the selected hybridoma cells. The animal immunization step always chooses rats and mice as immunized animals. The immunization plan depends on the different features of antigens, and a suitable plan is a critical link to make the cell fusion hybridization successful and to get high-quality mAb. After getting the splenic cells from immunized animals, these cells start cellular fusion with the prepared same-species myeloma cells. Cellular fusion is random in these two cells, therefore, the hybridoma cells have many different types. To get the target hybridoma cell, these cells should be sifted by known antibodies. The selected cells are injected into the abdominal cavity of the same species as the immunized animal to clone and then used to manufacture the mAb.

3.2. The Advantages of mAb Therapy

Compared with common NSCLC treatments, the mAb therapy has more advantages.

3.2.1. Compared with surgical resection

The surgical resection applies to the early stage of NSCLC, and once the patient has metastatic carcinoma or is at a late stage of cancer, this therapy is hard to clean all the tumors. Meanwhile, the surgical resection will cause a big trauma after the operation, which takes a long time to recover and they might catch postoperative complications during the recovery. The mAb is an injection therapy, and it has a wide range of applications, including early-stage and late-stage patients, diffuse NSCLC, and metastatic carcinoma.

3.2.2. Compared with radiotherapy

Radiotherapy uses high-energy radiation to clean local NSCLC, as same as surgical resection, radiotherapy can not clean up metastatic carcinoma, and diffuse cancer. The radiotherapy may cause the exposure area to catch inflammation, and this seriously influences the function of local tissues and organs. While the mAb only caused light gastrointestinal reaction or skin reaction. This reaction will not affect the function of specific organs, which improves the safety index of the mAb therapy.

3.2.3. Compared with chemotherapy

Chemotherapy is effected on the dividing cells, therefore it also kills the normal cells in the body, which will cause serious side effects. These side effects such as air loss, nausea, vomiting, myelosuppression, etc. Severely reduce the life quality of the patients. The mAb therapy only works to target antigens on the surface of the tumor cells, and this will greatly reduce the severe side effects and increase the safety of cancer treatment. Meanwhile, the living quality has significantly improved.

3.3. Recent Research Findings

Recent research findings are centered on the treatment of metastatic carcinoma and the combination of therapy with other common therapies. Delbari P. etc. al show that the anti-PD-1/PD-L1 mAb is effective in NSCLC brain metastasis, and the OS, PFS, and responsible rates in this research show that anti-PD-1/PD-L1 mAb has excellent efficacy and safety to these patients, especially those who have high PD-L1 expression [6]. Meanwhile, Dou XJ, etc. find that the combination therapy with anlotinib and PD-1 block date-monoclonal antibodies provides significant efficacy and tolerable safety, and this will provide a novel therapy for clinical NSCLC treatment [7].

4. Immune Checkpoint Inhibitors（ICIs）

4.1. Therapeutic Mechanism of ICIs

The immune checkpoint is a series of molecules expressed by cytokines to regulate autoimmunization so that the immune system cannot be overactivated. The tumor cells can express some molecule substances to activate the immune checkpoint in order to stop the antigen presentation into T cells and inhibit the immune function of T cells. In this way, the tumor cells can escape from the immune surveillance and survive. ICIs are inhibitors that can stop the immune checkpoint from working and reactivate the immune cells to clean the tumors.

4.2. Advantages of ICI Treatment

ICIs are working on the immune system, instead of the specific targets in the tumor cells, therefore, ICIs can treat many different types and periods of NSCLC. Meanwhile, it provides an effective treatment to those patients who are in poor physical condition or can not accept chemotherapy and surgery. ICIs can also significantly prolong the progression-free survival and overall survival of the NSCLC patients [8]. Compared with chemotherapy, the adverse reaction spectrum of ICI treatment is different. The ICI treatment is safer and has a higher tolerance to patients, which can improve the quality of life for the patients. ICIs attack the tumor cells by activating the immune system, and it can help the body produce the immune memory, therefore, the immune system of some patients can still recognize and kill the tumor cells after discontinuing ICI treatment, which gets long-term clinical benefits.

4.3. Recent Research Findings

Scientists are finding a lot of novel immune checkpoints and signaling pathways, for example, Tao found that MALT1 overcomes the resistance of ICIs through its paracaspase and death domains [9]. Meanwhile, the combination therapies with other treatments are research hotspots, like the research of Abushanab AK, etc. has found that the efficacy of ICI with taxane shows a significant improvement in NSCLC patients compared with the ICI or taxane monotherapy [10]. In the evaluating ICI therapeutic efficacy field, lots of biomarkers are found to evaluate the therapeutic efficacy more accurately. Liu J etc. has found novel biomarkers, GP73, a Golgi apparatus membrane protein, which will provide a potential biomarker to evaluate the efficacy of ICI therapy [11].

5. Tumor Therapeutic Vaccines (TTVs)

5.1. The Definition and Therapeutic Mechanism of TTVs

5.1.1. The definition of TTVs

TTVs a novel biological agents that inject the tumor antigens into the patient's body to activate the immune system and to induce the specific immune response to the tumor cells so that it can realize the goals of cleaning the tumors and preventing the tumor recurrence and metastasis.

5.1.2. The therapeutic mechanism of TTVs

When the tumor antigen of TTV gets into the body, the antigen-presenting cells intake and process them, and then present them as an antigen-peptide-MHC complex form on the surface of cells. The TRCs on the surface of T cells recognize the antigen-peptide-MHC and activate the CTL and the Th. CTL can recognize the antigen on the tumor and release cytotoxic substances to kill the tumor cells, while the Th cells secrete IL-2 etc. cytokines and further activate CTL and NK cells to improve the clearance of tumor cells by immune cells. With the effect of TTVs, the immune system will produce immune memory cells and these memory cells will exist for a long time and make a quick response in the case of finding the same tumor antigen to keep on monitoring and killing the tumors in the long term.

5.2. The Development Progress of TTVs

Many different types of TTVs are in research and development. TTVs are based on the ADCC theory and have many different types, like whole cell vaccine (WCV), tumor peptide vaccine (TPV), and genetically engineered vaccine (GEV). The TPV has strong specific and high safety, and the novel generation TPV can activate CTL and the Th effect at the same time. The GEV activates the specific immunity of the body, and it is a hotspot in the research field. Meanwhile, the mRNA vaccine is widely applied in anti-tumor treatment, and it has significant development in solid tumor treatment. Compared with DNA vaccine, mRNA vaccine can translate in the cells both in the dividing phase and not in that phase and it will not integrate into the genome causing insertion mutation.

5.3. The Limitations and Challenges in the Clinical Application of TTVs

TTVs still have a lot of limitations and challenges in clinical applications. The tumor cells have high heterogeneity, the tumor cells in every patient are specific and the surface antigen may exist in difference, and this is hard to find a TTV that can cover all the tumor cell antigens, which makes the vaccine not work well for several tumor cells. Meanwhile, the tumor cells can escape from immunologic surveillance and aggression through many mechanisms, therefore, even though the TTV can activate the immune system, the tumor cells still have a chance to escape from the immune cells and impact the efficacy of TTVs. More than that, how to deliver the antigen into the tumor session and the antigen-presenting cells, how to use the TTV the patients in different stages the safety of TTVs, the administration, and the dosing frequency are also unknown and the need to research. The most important and practical limitation is that the research and the production of a TTV are complex and need a lot of time and high cost, which makes TTVs hard to promote into clinical applications.

6. Conclusion

This article talked about the basic pathogenesis of NSCLC and the immunotherapy of NSCLC. It discussed mature monoclonal therapy, immune checkpoint inhibitors therapy, and tumor therapeutic vaccine therapy. It introduced the mechanism and the recent research findings about these therapies, including the combination of mAb and ICIs with conventional therapies. Compared with conventional therapies, immunotherapies have fewer adverse reactions and have higher security and accuracy. This article also talked about the limitations of TTVs, and it can provide some references to the TTV research. Meanwhile, it can also provide references to NSCLC clinical treatment. Therapies like ICIs and mAbs are developing fast and level to mature to apply clinically, however, limitations of these two therapies still exist, and this article did not mention them. The NSCLC is still a serious and not to be underestimated tumor in the whole world. Immunotherapies are one of the treatments and there are more and more treatments found by researchers and applied to clinical patients. To decrease the incident rate, the most significant project is preventing the incidence of NSCLC, like banning tobacco, protecting the respiratory tract in a dusty working environment, etc. Prevention and treatment of NSCLC are both worthy of attention.

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