

Research progress of monoclonal antibody in the treatment of lung cancer

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Abstract. The largest cause of cancer-related deaths is lung cancer. Conventional therapies like chemotherapy, surgery and radiation therapy have been widely used in treating cancer including lung cancer. However, the fact is that these conventional therapies may generate severe adverse effects. For example, they are lack of specificity, they could not treat the target tissue specifically. When processing these conventional treatments, adjacent normal cells and tissues may be harmed. With this kind of problem in treating lung cancer, more and more therapeutic drugs and therapies are being develop to reduce such problems. Monoclonal antibody treatment is an example. Since the concept of magic bullet had been introduced by Pual Ehrlich, scientists have been inspired to conduct further and deeper research into monoclonal antibody treatment. In this concept, antibodies are said to be magic bullets since they are useful tool to treat foreign cells. Since then, scientists had been devoting themselves to the development of monoclonal antibodies. These days several monoclonal antibodies are FDA approved. Since monoclonal antibodies work through various mechanisms, it plays an important role in cancer therapies. One monoclonal antibody is specific to only one type of antigen and it works by trigger the immune system. Monoclonal antibodies would become the focus of future research.

Keywords: monoclonal antibody; lung cancer; immunotherapy.

1. Introduction

These days, more and more diseases and pandemics are arising, causing threats to human's lives. In order to improve human health level, scientists are still devoting themselves to the development of therapies for various diseases including but not limited to lung cancer. Cancer is an extremely diverse illness that is primarily brought on by the accumulation of genetic and epigenetic alterations that result in abnormal and uncontrolled cell growth [1]. Lung cancer is when these changes happen in lungs. The most common cancer that results in high mortality rate is lung cancer [2]. Despite significant advances in numerous medicines, lung cancer survival is extremely poor and has scarcely improved recently [2]. Looking through standard therapies for cancer such as chemotherapy, surgery and radiation therapy, adverse effects may arise. Meanwhile, rapid developments are seen in immunotherapies such as monoclonal antibodies which have become a significant class of therapeutic drugs available today since they produce less adverse effects and are more effective due to its high specificity [3]. They are mainly produced by two types of techniques which are hybridoma technique and phage display. Monoclonal antibodies are proteins with quantenary structure that composed of two light and heavy chains connected by disulfide bridges and forms constant and variable regions [4]. Clones of B cells create different types of monoclonal antibodies that bind to different epitopes on an antigen.

Lung cancer is the main cause of morbidity and mortality. The number of lung cancer patients is rising sharply every year. Among the many therapeutic approaches, monoclonal antibodies appear to be the most significant in reducing mortality and increasing cure rates. At the same time, the monoclonal antibody has been widely used in clinical trials and some achievements have been made. By immunizing mice and hybridoma with tumor cells isolated from human lung cancer tissue, the

lung cancer high-capacity functional monoclonal antibody library has been expanded to more than 4000, among which 39 strains of monoclonal antibody against lung cancer membrane protein are positive with lung cancer living cells. When a lung cancer patient reaches an advanced stage, conventional chemotherapy or radiation therapy can no longer eliminate the tumor cells. Other treatments, such as targeted therapies, are needed. Typically, monoclonal antibodies are used at the end of cancer, either alone or with chemotherapy. Advances in monoclonal antibodies have also been seen in some clinical trials. Cetuximab, for example, improved survival rates when given to patients with advanced lung cancer. However, most patients will experience some side effects after using antibodies, which can be severe or mild. Therefore, it is suitable to pay attention to the physical condition of the patient.

This paper introduces basic information related to monoclonal antibodies including but not limited to mechanisms and the background to develop monoclonal antibody drugs. And it will focus on the application of monoclonal antibody drugs in treating lung cancer by showing how they work and compare with conventional treatments. Meanwhile, this paper would also examine the limitations of using monoclonal antibodies and the challenges it faces.

2. Monoclonal antibody therapies related to lung cancer

The application of monoclonal antibodies (MAbs) in medication had developed nearly half of century from murine, chimeric to full humanize antibody and overcome the problem of immunogenicity [5]. Currently, MAbs medicines has reached an indispensable position in multiple fields.

2.1. Immunotherapeutic

Surgery, chemotherapy or radiotherapy were once the standard treatments for lung cancer [6]. However, the limitations of these treatments and the fact that the cancer has already developed by the time most patients seek medical advice, lead to a 5-year survival rate of 5% and an unsatisfactory prognosis for lung cancer [7]. Currently, immunotherapeutic become the most popular treatment for lung cancer [6].

Immunotherapeutic are categorized into two different kinds, passive immunotherapy and active immunotherapy, both of them aiming to reinforce the natural defense of patients to cancers [6]. Passive immunotherapy is considered as using MAbs medicines to damage the cancer cells directly [8]. Active immunotherapy aims to activate patients own immune system to eliminate the cancer cells [6]. A successful immunotherapy must activate the anti-tumor immune response and reduce the immunosuppression effect which caused by tumour [6].

2.1.1 EGFR and ALK

Anti-EGFR and anti-ALK medicines were once brought the hope for the patients of NSCLC [7]. The mutation and or rearrangement of these two specific genes are considerate responsible for the proliferation of tumor and the cancerization of body cells [9]. To the NSCLC that possess these two genes are highly curative to the target therapy of tyrosine kinase inhibitors (TKIs) [9]. However, there is nothing that can be done for patients who do not have these two specific genes or whose cancer is not caused by these two specific genes [7]. Studies have shown that only 15% of NSCLC involve EGFR mutations and only 3-7% are positive for ALK rearrangements [9], so anti-EGFR and/or ALK drugs are not common.

2.1.2 PD-1 and PD-L1

After years of effort, the application of anti PD-1 and or PD-L1 brought cancer therapy into a new level. The immune system is considered to be an important way to prevent normal cells from becoming cancerous, however, the immune response of tumor cells is limited by many factors and cannot induce an immune response against tumor cells [7]. PD-1 and PD-L1 are a group of immune check points and they are also the surface receptors that deliver on T cell, B cell, TIL and various

immune respond-related organism. Immunosuppressant activates anti-tumor immune responds by intercept immune check points, furthermore inducing and activating the proliferation and immune responds to certain immune cells [7].

Additionally, cytotoxic lymphocytes (CTLs) have also played an important role in immunotherapy, multiple studies suggest there is a great number of CTL in tumor-infiltrating lymphocytes (TIL) [6]. TIL is able to enter the cancer cell which it originates, that is the prerequisite of any immune respond to cancer [6]. The complex that is produced during the process of the combination of PD-1 and PD-L1 could lead to the suppression of CTL reaction and furthermore lead to the incapacitation of anti-tumor immunity [6]. Using PD-1 and or PD-L1 inhibitor could restore the anti-tumor immunity by suppression the process of the combination of PD-1 and PD-L1 [7].

2.2. Proposed therapies for lung cancer

2.2.1 Inhibition of tumor angiogenesis

Bevacizumab is the first approved drug to inhibit tumor angiogenesis, which can inhibit the formation of new blood vessels and achieve anti-tumor effects [10]. Researches have investigated that Bevacizumab can be used to treat patients combined with the thoracic perfusion chemotherapy [10]. Use B-ultrasound to locate the location of pleural effusion, and then place a central venous catheter for thoracic drainage treatment to drain the pleural effusion as clean as possible [10]. After completing the drainage, inject 50 mg of cisplatin and 20 ml of 0.9% sodium chloride injection into the chest cavity- The research group used B-ultrasound to locate the pleural effusion and placed central venous catheter for thoracic drainage treatment to make the pleural effusion as clean as possible [10]. After drainage, 50 mg cisplatin and 0.9% sodium chloride injection 20 ml were injected intrapleural. The comparison of tumor treatment efficacy shows that the total tumor control rate of patients treated with this method is 77.14% [10]. It is 51.43% higher than using only thoracic perfusion chemotherapy [10]. Another plan has been proved to be effective in the treatment of lung cancer, is using Nitozumab combined with paclitaxel and carboplatin [11]. Paclitaxel is a diterpenoid alkaloid compound with excellent anticancer effects, and has been widely used in clinical treatment of various tumor diseases in recent years [11]. Carboplatin belongs to platinum compounds and is a broad-spectrum anti-tumor drug with certain therapeutic effects on various tumors [11]. Nitozumab is a novel monoclonal antibody drug targeting epidermal growth factor receptor, which can effectively inhibit the proliferation and neogenesis of vascular endothelial cells in cancer tissue, thereby exerting anticancer effects [11]. An investigation was carried out to give evidence for the efficacy of this plan [11]. It investigated two groups of patients, with group one, using these three substances together; and group two, using paclitaxel and carboplatin only [11]. Before chemotherapy, both groups of patients were injected with dexamethasone intravenously at a dose of 10mg; Diphenhydramine intramuscular injection, injection dose 50mg; Cimetidine is injected intravenously at a dose of 300mg. Preventing patients from developing allergic reactions to paclitaxel. Both of the two groups had been observed and taken data during a treatment cycle, and the results were made according to the comparison of serum tumor marker levels between two groups of patients before the treatment. The results illustrated that the rate of controlling the lung cancer in group one is much higher than that in group two, which has a difference of about 20% [11].

2.2.2 Photodynamic therapy (PDT)

Photodynamic therapy is a type of therapy that is used in lung cancer treatment. It uses light as the main part of the treatment. Studies have shown that for some inoperable cancer PDT may help to extend the life expectancy [12]. PDT is mainly composed of three parts: photosensitizer, light, and oxygen, from which they combined together to produce non-ionizing electromagnetic irradiation [12]. Photosensitizer is usually a type of dye which act as catalyst that can absorb light of specific wavelength [13]. Singlet oxygen in PDT therapy is the most important thing to kill cancer cells since it generates anti-cancer effect by inducing apoptosis, necrosis or autophagy [14]. PDT was originally utilized in 1982 to treat NSCLC in order to induce tumor necrosis and airway reopening [14].

Compared to alternative methods or either treatment alone, PDT with chemical or radiation can prolong local tumor control [12]. In treatments of using PDT, the process is less invasive compared with surgery and it has higher specificity and generated minimum adverse effects on adjacent normal tissue while the PDT therapy itself is cost-effective [12]. Similar to traditional lung cancer treatments, PDT minimizes side effects but also has drawbacks. Limited penetrating ability of visible light can cause it unable to target tumors in deeper locations as well as the limited amount of oxygen around tumors which may significantly reduce the efficiency of PDT therapy [12].

2.2.3 Antibody-drug conjugate (ADC)

ADC using monoclonal antibodies as carriers, coupled with biologically active cytotoxic molecules, such as nuclides, toxins and chemical drugs [5], by chemical linkers and deliver them to tumor cells and entering the cell through endocytosis and binding with lysosomes to release toxins [13]. In current clinical treatment, all ADCs are not oral medicines but enter the body by intravenous administration to avoid the inactivation of medicines that caused by gastric enzymes [14]. Trastuzumab deruxtecan is a ADC that mainly applied in the treatment of cancers that possess HER2. The variation of HER2, such as mutation, over-expression, expansion, could induce the cancerization of normal cells [15]. The ratio of HER2 that are present in NSCLC are 1% to 4% (gene mutation), 2% to 5% (gene amplification), and 2% to 30% (protein overexpression) [16]. The composition of trastuzumab deruxtecan can be roughly divided into two parts, trastuzumab and DX-8951 derivative, DXd (A novel topoisomerase I inhibitor camptothecin derivative), these two-part coupling together by a tetrapeptide linker which can be braked by specific enzymatic hydrolysis [17]. The trastuzumab part can specifically binds to HER 2 receptors on the surface of cancer cells and allowing Trastuzumab deruxtecan enter the cancer cells by endocytosis [17]. Etrapeptide linker will be hydrolyzed by the lysosomal enzymes and release the DXd to inhibit the activity of topoisomerase I after the medicines enter the cancer cells [17].

3. Side effects of Treatment using Monoclonal Antibodies

3.1. Resistance

Though monoclonal antibody medicines provide a bright future for related patients, multiple side effects including innate or acquired resistances are still problems. For example, the monoclonal antibody medicines that are based on the target spots of EGRF and or ALK are resisted by lung cancers which cannot be attributed to the mutation of genes EGRF and or ALK or the patient who does not have any of them (EGRF and or ALK). Furthermore, antibody-drug conjugates (ADC) provide an ideal method to transfer toxins to cancer cells. However, nearly every ADC will develop drug resistance. Resistance to the particular ADC typically develops during the course of treatment and is typically related to variations in the target antigens, antibody endocytosis, transport pathways, alterations in the cell cycle and the signaling pathways that regulate them, lysosomal function, and off-target effects of cytotoxic molecules [13].

3.2. Cytokine-release syndrome

CRS is a systemic severe inflammatory response that could threat patients' life in the worst scenario [18]. The symptoms, including fever, chills, hypotension, and tachycardia, could be usually observed immediately after the indigestion of medicine. During a clinical trial of Blinatumomab, 2% of volunteers were presented as grade 3 CRS among 189 patients [18].

3.3. Central nervous system events

Over 50% of patients who have received a Blinatumomab treatment have experienced central nervous system events, such as tremor, encephalopathy and cerebellar alteration phase during a phase 2 study [19]. Besides the common symptoms caused by central nervous system events some deadly brain edema has also been observed among those patients [18]. Though the mechanism of the events

is still unclear but few articles suggest that inflammatory cytokines may be involved during the process [18].

4. Humanized modification of murine antibody

As a very common laboratory animal, mice are very conducive to the study of antigens and antibodies. Therefore, in the monoclonal antibody experiment, the researchers chose to use mice. The first is that mice have a high-affinity characterization and can easily produce monoclonal antibodies. Second, when the gene carrying the humanized immunoglobulin is inserted into the mouse, it can produce complete antibodies and complete immunoglobulin. Finally, the variable domain and the humanoid constant domain can be defined to have effector functions [20]. However, these antibodies from mouse sources also depend on many different factors, such as application method, dose, binding reaction performance, and so on. Even though human control is possible in these factors, there is a strong human anti-mouse antibody response in early antibody sequences. This has seriously affected the use of murine-derived antibodies in clinical trials. Hence the need for murine antibodies and the need for technological modification [5].

The first technology is called hybridoma technique. The hybridoma technique was developed by Kohler and Milstein in 1975. By fusing antibody-producing cells with myeloma cells to produce Ab with any specificity. The technology is not just widely used in clinical trials. It is also used in immunotherapy for many cancers, organ transplants, and so on [21]. For example, this technique was used to test the immunogenicity of 131I-TNT in patients with advanced lung cancer. The study concluded that immunogenicity was present in only a small number of patients [22]. Another study is investigating the efficacy and toxicity of 131I-chTNT in patients with advanced lung cancer. The tumor necrosis treatment used in this study was a recombinant chimeric TNT antibody to obtain a therapeutic dose in combination with radionuclide iodine-131. This does not require a precise location or type of tumor. It is concluded that 131I-chTNT is well tolerated and can be used in local or systemic refractory lung tumors [23].

Secondly, it's a technique to improve affinity, which is called surface remodeling antibody theology. Surface remodeling technique is to humanize mouse antibody design by using computer molecular design and surface residue replacement. Of course, this needs to be based on the analysis of the spatial structure characteristics of antibodies and the interaction between residues. Since non-human differential residues of murine antibodies are exposed in the variable region, sequence analysis and structural analysis are required to obtain this data. Finally, the residue site to be mutated can be determined [24].

Finally, the modified antibody technique is to transplant and reconstruct CDRs and Specific Determinant Region. After the mouse antibody variable region genes were transplanted into the corresponding framework region of human antibodies, only about 6% of the sequences were mouse genes. In other words, heterogeneity decreases, humanization of new antibodies increases, and immunogenicity decreases [5].

5. The application in clinical pipeline

Monoclonal antibodies (mAbs) are a kind of biological product. It is a compound made by the immune system to treat some cancers or inflammations. Between biological drugs and synthetic drugs, biological drugs have more complex mechanisms of action and synthetic drugs are purer [25]. The clinical pipeline development is the essential new trend of monoclonal antibodies. Furthermore, monoclonal antibodies come in a wide variety of forms. However, it is clear that human monoclonal antibodies have improved over other chimeric or humanized antibodies. 2013 was a big year for monoclonal antibodies. Because that was the year it got its first approval and its first market debut [26]. After 2013, the development of monoclonal antibodies can be seen to have significantly improved. Every year, the number of new antibody therapies approved continues to increase [27].

Through some studies and experiments, such as transgenic mice and phage display techniques, some new monoclonal antibody techniques, such as whole human antibodies, have been discovered. Although the research was quite successful, the development process was too difficult. According to an experiment in 1985 about transgenic mice, researchers used human V-genes to supersede the native immunoglobulin repertoire and infused the desired antigen into the transgenic mice to find some antibody genes by some selection technologies. It is a new novel theology in the production of fully human monoclonal antibodies. In 2006, people used Abgenix Xeno Mouse technology to develop the first fully human antibody, Vectibix. The next novel theology is phage display technology. This technology was initially reported in 1985. Because these bacteriophages have numerous extensive peptide and protein libraries on their surface, researchers inserted the foreign peptide sequence into the phage genome. Once the selection process has concluded, after a few weeks, scientists can extract and identify the cognate genome following amplification. However, researchers found fully human monoclonal antibodies have some severe drawbacks when used in treating patients. In order to promote novel monoclonal antibodies that can avoid these serious limitations, researchers discovered recombinant antibody engineering approaches. These techniques include Fab, single chain fragment variable (scFvs), "Miniaturized" full-size mAbs, antibody-radionuclide conjugates, and others. Compared to other categories of antibody fragments, Fabs are the most popular and account for more than 49% of the segment under active clinical development. Different Fabs are created by several companies to cure conditions like lung cancer diagnosis, severe Crohn's disease, and clot prevention. The single chain fragment variable is also another useful antibody fragment category. Blinatumomab, a bispecific T-cell antibody against CD19, is an illustration of the single-chain fragment variable. To obtain maximum efficacy and minimize side effects, patients require continuous intravenous infusion of the antibody during treatment. Blinatumomab links T-cell-specific cd3 and B-cell-specific CD19 to exert cytotoxic activity on target cells. The FDA authorized blinatumomab for ALL treatment in 2014. The following new type of antibody fragments is known as "miniaturized" full-size mAbs. Trubion Pharmaceuticals' compact modular immunopharmaceuticals are the best example of miniaturizations. There are some differences between single chain fragment variables and it. The tiny modular immunopharmaceuticals only have one "effectors" domain that is constant and one each of the VL and VH antigen binding domains. As a result, SMIP lost the immune effector function. For the pipeline development, SMIP only accounts for 4%. The most advanced SMIP development project, TRU-015, is an anti-CD20 created in partnership with Wyeth. Antibody-radionuclide conjugates make up the final new category. This approach relies on the use of monoclonal antibodies, which can improve cancer therapy and imaging. Additionally, the link between monoclonal antibodies and radionuclides is shown by antibody-radionuclide [28]. However, this antibody fragment class has certain requirements for patient use. Patients need to do a diagnostic test to check if their radioimmune conjugate is compatible with the imaging procedure. If they pass the test, they will receive an injection of a therapeutic medication that contains the same antibody and is labeled as an effective radionuclide.

6. Conclusion

Lung cancer is a malignant tumor disease with a high incidence rate and a high mortality rate. The pathogenesis of this disease is not yet clear in clinical practice, and its early clinical manifestations are lack of obvious characteristics. After examination and diagnosis, the focus can be removed in time through surgery. However, because patients usually have no symptoms of physical discomfort at the beginning of the course of disease, they are prone to miss the best opportunity for surgical treatment, leading to the development of the late course of disease at the time of diagnosis. Advanced lung cancer patients are more likely to experience distant metastasis and spread of the disease, making them ineligible for treatment with traditional surgical techniques. Currently, patients with advanced lung cancer frequently get chemotherapy in clinical settings. It is undeniable that these conventional therapies, due to their lack of specificity, can bring many problems. Ordinary cells and tissues are

also likely to be harmed indiscriminately during the treatment process. Therefore, the application of targeted monoclonal antibodies is an effective way to solve these problems, according to what this paper has mentioned, and other authoritative researches. In the future, investigations on the use of monoclonal antibodies in lung cancer treatment and other chronic diseases will become one of the main areas of scientific researches. More and more new, effective treatment plans may present, bringing more convenient conditions to medical field.

Author contribution

All the authors contributed equally, and their names were listed in alphabetical order.

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