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Research Progress of Biosimilars of Monoclonal Antibody Drugs For The Treatment of Tumors

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Abstract. Monoclonal antibodies (mAbs) have gained prominence in cancer treatment due to their targeted therapeutic mechanisms, offering fewer side effects compared to traditional chemotherapy. Despite the advancement in original mAb-based anticancer drugs, the high costs associated with these therapies pose a significant challenge, especially for low- and middle-income countries. This has led to an increased focus on developing biosimilars, which are more affordable alternatives with similar therapeutic effects. This paper reviews the research progress of mAb drugs and their biosimilars for tumor treatment, highlighting the clinical impact of mAbs targeting common cancer markers such as HER-2, CD38, and eEF2K. For instance, trastuzumab biosimilars have been shown to improve the pathological complete response rate (pCR) in breast cancer patients when added to neoadjuvant chemotherapy, demonstrating an approximate 15% increase compared to chemotherapy alone. The study concludes that while biosimilars provide a cost-effective and accessible alternative, there is still a lack of long-term clinical data and real-world efficacy, particularly for biosimilars targeting newer cancer markers like CD38 and eEF2K. The paper highlights key advancements in biosimilar production, such as those of trastuzumab biosimilars, and discusses emerging targets like eEF2K, with potential for future therapeutic interventions.

Keywords: Monoclonal antibodies, biosimilars, cancer targets.

1. Introduction

In recent years, with people's growing demand for healthy and better life, research in the field of medicine and health has also received widespread attention. Although there have been some breakthroughs in the research and development of some new monoclonal antibody(mAb) anticancer drugs, the research and development of mAb-based anticancer generic drugs is still an area that needs attention. For the use of original anti-cancer drugs, people in low-income and middle-income countries around the world find it difficult to afford the high cost of drugs. At the same time, the high cost of purchasing original drugs also brings a heavy burden to the medical care systems of backward countries. MAbs can be used for targeted therapy against specific cancer tumor markers or cell markers to reduce damage to normal cells, and this drug has fewer side effects than traditional chemotherapy drugs. As of June 2024, the European Medicines Agency (EMA) has approved 48 mAbs and the U.S. Food and Drug Administration (FDA) has approved 56 mAbs for the treatment of cancer [1].错误!未找到引用源。 For generic drugs, the current mainstream ones are rituximab, tremelimumab, ipilimumab, novolumab, pembrolizumab and bevacizumab, which are all generic drugs approved for marketing in the European Union. Generic drugs occupy an important position in the Chinese market, accounting for about two-thirds of the pharmaceutical market. Taking trastuzumab as an example, its research progress is that adding trastuzumab to neoadjuvant chemotherapy can significantly improve the pathological complete response rate (pCR), which can be increased by about 15% compared with chemotherapy alone. Trastuzumab is more effective than traditional methods in the treatment of breast cancer patients [2].

Hence, In order to better utilize the advantages of mAb drugs in targeted cancer treatment, this article will introduce some targets and the mechanism of action of mAb drugs, and explore the relationship between mAb drugs and traditional chemotherapy drugs. This article will review the research progress of mAb drugs and their biosimilars for the treatment of tumors. This article will introduce

in detail the common targets in tumor treatment and their corresponding mAb drugs, and explore the mechanism of action of these drugs and some of their clinical applications. Secondly, this article will focus on analyzing the research and development status of biosimilars for various targets, including their production technology and research and development process.

2. Target HER-2

2.1. Mechanism of Action of HER-2 Target in Breast Cancer Treatment

Human Epidermal Growth Factor Receptor 2 (HER-2) is a protein encoded by the ERBB2 gene and is also an important breast cancer target. HER-2 is a member of the epidermal growth factor receptor family and is often overexpressed in breast cancer, leading to rapid proliferation and metastasis of tumor cells [3]. Normally, HER-2 is a protein that is involved in the cell growth process and is used to repair and maintain the growth state. When the HER-2 receptor is overexpressed, it can bind to more growth factors to form more dimers [4]. In this case, the transmission intensity and frequency of the signal pathway in the cell will be enhanced, causing the cell to continue to receive proliferation signals and cell division to be out of control, which leads to the rapid growth of cancer cells. The RAS/MAPK and PI3K/AKT signaling pathways are important for transmitting membrane receptor signals to the interior of the cell, where the receptor signals are transmitted and acted upon by these signaling pathways[5]. Ras is activated after binding to GTP, recruiting Raf to the cell membrane and binding to it. MEK and MAPK are then phosphorylated and activated in turn. The activated MAPK can regulate a variety of transcription factors and protein kinases, thereby inducing cell proliferation, differentiation and other reactions. For the PI3K/serine-threonine protein kinase pathway, along with receptor activation, two different subunits of PI3K can be activated simultaneously. In this way, the effect of activating PI3K is achieved, and PIP2 on the membrane is converted into PIP3. PIP3 can become a second messenger to recruit more Akt and PDK1 to the cell membrane, thereby activating Akt, which promotes the metabolism and growth of cancer cells [6].

2.2. mabs for the Treatment of Positive Breast Cancer

High expression of HER-2 is widely considered to be an important adverse factor for positive breast cancer and an important indicator for breast cancer assessment.HER-2 positive breast cancer is highly correlated with the deterioration and high recurrence rate of cancer cells. Inhibition of HER-2 receptor dimerization has become an important breakthrough in targeted anti-cancer drugs for breast cancer [7]. Trastuzumab is the first humanized mAb for breast cancer, and it plays a leading role in the treatment and prognosis of breast cancer. It can effectively reduce the mortality rate of breast cancer patients and prolong the 5-year survival rate. The main mode of action of this monoclonal antibody is to preemptively bind to the HER-2 receptor and prevent it from forming dimers, thereby reducing the establishment of intracellular signal transduction pathways and inhibiting the unlimited proliferation of cells to achieve the goal of alleviating the growth of cancer cells [8,9]. So far, the use of trastuzumab has brought a treatment direction to the treatment of breast cancer, but it is only applicable to breast cancer-positive patients.

2.3. Research Progress of Biosimilars

Currently, doctors mainly use trastuzumab to treat patients with positive breast cancer. Trastuzumab can bind to the HER-2 receptor with very high specificity, preventing the rebinding of EGF and HER-2, thereby delaying the growth of cancer cells. For various cancer treatment drugs, high R&D costs are accompanied by a high-risk R&D process, and the development of trastuzumab is no exception. According to a recent study, trastuzumab, as an imported drug, is relatively expensive in the Chinese market, with a course of treatment costing as much as 300,000 yuan, or about 42,000 U.S. dollars[10]. This is mainly because of the huge cost of drug development, which is a fundamental problem. Secondly, the prices of a series of production materials such as raw materials and auxiliary materials have risen. Taking another approach, if the development and research costs of trastuzumab (original

drug) can be reduced or even eliminated, the price of the drug will become low. The solution is to develop generic drugs and put them into mass production.A study explains that when the willingness to pay threshold is 3 times China's per capita GDP in 2023, the market for original drugs is much smaller than that for biosimilars, which is reflected in the sensitivity analysis: the increasing willingness to pay threshold leads to the probability of the economic feasibility of trastuzumab biosimilars tending to 100%.In actual medication effects, comparative experiments show that the two drugs are almost the same. The kinetic parameters, effectiveness and drug safety are almost the same [11,12]. Biosimilar trastuzumab has good economic benefits in the treatment of recurrent or metastatic HER-2-positive breast cancer.

3. Target CD38

3.1. The Role of CD38 Targets in Cancer

Until today, multiple myeloma is a difficult disease to cure. Because of the high expression of CD38 in multiple myeloma, it has become a marker for drug targeted therapy. CD38 is a transmembrane glycoprotein that is expressed to varying degrees in normal bone marrow, whether in myeloid or B lymphoid precursor cells, or mature lymphocytes, monocytes, and granulocytes. However, in multiple myeloma cells, the expression level of CD38 is significantly higher than that of normal lymphocytes and bone marrow precursor cells, showing extremely high positive expression [13]. CD38 protein affects the progression of multiple myeloma by regulating the concentration of intracellular calcium ions. CD38 can promote the catalysis and production of cyclic ADP ribose (cADPR), which is an important signal transduction molecule in cells that can stimulate the proliferation potential of cells. Cancer progression will occur in cancer cells that express a large amount of CD38 protein.

3.2. Effects of Monoclonal Antibody Drugs on CD38 Target

There is a small amount of expression on the surface of lymphocytes, red blood cells and platelets, but in almost all multiple myeloma cells, CD38 protein is highly expressed. It is a type II transmembrane glycoprotein with a molecular weight of 46 KDa and is highly expressed in bone marrow cells after canceration. There are documented cases where researchers used daratumumab, which was previously used to treat malignant blood diseases, to treat multiple myeloma [14]. However, daratumumab infusion may cause patients to have positive red blood cell antibody screening and cross-matching incompatibility. This may cause difficulties in subsequent red blood cell transfusions. The advantage lies in the treatment of multiple myeloma, daratumumab has a good effect and has a positive effect on the apoptosis of myeloma cells. Daratumumab is the first CD38 mAb approved for the treatment of multiple myeloma and is often used in combination with other drugs to treat patients with early or relapsed disease. Daratumumab binds to CD38 on the surface of multiple myeloma cells, activating complement, natural killer cells and macrophages in the host immune system, thereby inducing complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). These mechanisms work together to ultimately lead to the death of malignant myeloma cells. In addition, Fcγ receptors play a key role in signal transduction in this process, further enhancing the anti-tumor effect [15].

3.3. Drug Evaluation

Daratumumab is an innovative mAb targeting CD38, so it is a biologic. Compared with chemical original drugs, biologic generics have higher manufacturing standards and only have minor differences in production processes. Therefore, there are no biosimilars on the market worldwide. Precisely because daratumumab has significant and lasting effects on different subgroups of patients, as the experimental time gradually lengthens, the effects become more obvious [16]. Many pharmaceutical companies are developing biosimilars of daratumumab to reduce drug costs for

patients. As research and development progresses, multiple biosimilars of daratumumab will be able to enter the market in the next few years, such as the one currently being developed by Amgen.

4. Target eEF2K

4.1. Profound Targets for Cancer Treatment

For some common cancers, researchers are always trying to find more ways to treat them, including discovering new targets. eEF2K, as a new target for the development of cancer drugs, was first discovered by Nairn in 1985. eEF2K belongs to the α-kinase family and is the only calcium/calmodulin-dependent protein kinase in the family [17]. eEF2K is highly expressed in a variety of cancers and plays important roles in tumor growth, cell cycle, autophagy, apoptosis, angiogenesis, invasion and metastasis. Similar to the targets of the signaling pathways mentioned above, eEF2K regulates cell growth and survival by inhibiting protein synthesis. In cancer cells, high expression of eEF2K can promote the progression of the cell cycle and angiogenesis (the formation of blood vessels is a sign that cancer cells are about to obtain more nutrients from the host body), thereby providing necessary growth signals. At the same time, this kinase will help cancer cells survive in adverse environments, increase invasiveness and metastasis. These mechanisms together promote the growth and spread of cancer cells. In the process of studying the growth and migration of gliomas, researchers found that eEF2K can slow down protein synthesis under hypoxic conditions, helping cells save energy, thereby promoting the proliferation and progression of tumor cells. In disguise, it promotes the deterioration of gliomas [18], especially when some patients are treated with cancer cell growth-blocking treatments to help cells save energy and play an antagonistic role.

4.2. Progress in Manufacturing Generic mab Drugs

Drug development revolves around how to more effectively inhibit the promotion of cancer cell growth by eEF2K. This idea is to prevent the promotion of cancer cells by eEF2K and accelerate cell apoptosis. BL-EKI03 is a newly discovered eEF2K inhibitor that promotes autophagy and apoptosis in breast cancer by inhibiting the activity of eEF2K. BL-EKI03 can activate apoptosis signaling pathways, such as causing mitochondrial dysfunction and activating caspase, leading to programmed cell death, thereby achieving the effect of treating cancer. The specific mechanism is that BL-EKI03 can cause a decrease in mitochondrial membrane potential, which directly affects the increase in intracellular calcium ion concentration, thereby activating pro-apoptotic proteins (which is also a self-defense mechanism of the cell), leading to cell apoptosis [19,20]. Furthermore, caspase is activated. The caspase series of enzymes are important undertakers of cell apoptosis and can further promote cell apoptosis. However, the inhibitor BL-EKI03 is in the research stage, mainly focusing on pre-clinical trials and early clinical trials. Although BL-EKI03 has shown potential in cancer treatment models such as breast cancer, it has not yet become an approved drug on the market. Therefore, there is no research progress on related generic drugs, but given that the long research process of the original drug has a high probability of resulting in high research costs, the development of generic drugs in the future is still necessary.

5. Conclusion

In conclusion, this paper has explored the development and impact of mAb drugs and their biosimilars in cancer treatment. The study argued that biosimilars provide a cost-effective alternative to original mAbs, which can make advanced cancer treatments more accessible, especially in lower-income regions. By reviewing recent research on common cancer targets like HER-2, CD38, and eEF2K, it has been shown that biosimilars, such as those developed for trastuzumab, hold significant therapeutic promise. These biosimilars are effective in mimicking the original drug's action, thereby offering more affordable options without compromising treatment outcomes. However, it is important to note that this study has limitations, particularly regarding the long-term clinical data and the real-world efficacy of certain biosimilars, such as those targeting CD38 and eEF2K, which are still in the

development stages. In the future, the direction that researchers should pay attention to is the comparison between generic drugs and clinical original mAb drugs. And we are constantly looking for new treatment targets to provide new ideas for treating cancer. In addition, it is also necessary to study how to further reduce the production cost of generic drugs and thereby reduce the burden on patients while ensuring that regulatory and approval standards remain unchanged.

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