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Research Progress of Mono- antibody Therapy for Breast Cancer

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Abstract. Breast cancer is the most prevalent form of cancer and the second greatest cause of death from cancer among female population. Traditional medication of breast cancer usually indicates anti-estrogen drugs and aromatase inhibitors. Monoclonal antibodies (mAbs) are a type of advancing immunotherapy that has become commonly used to treat cancers since it uses antibodies to target and destroy malignant cells specifically. Among them, trastuzumab is a humanized mAb derived from recombinant DNA. It can specifically react to the extracellular part of human epidermal growth factor receptor-2 (HER-2). Research proved inhibitory effect of trastuzumab on the proliferation of certain tumor cell, and is also a potential material for antibody dependent cell-mediated cytotoxic reaction. While there are a variety of forms in the disease, and each form has a unique assortment of surface antigens, making it difficult to treat with a single type of mAb. Therefore, further work is needed to develop monoclonal-based antibodies that can target multiple forms of breast-related cancer. Furthermore, researches trying to create mAbs that can be combined with conventional cancer therapies like radiotherapy and chemotherapy are still being done. Here we summarized recent researches on mAb therapy for breast cancer and discusses the challenges as well as the progresses in this area.

Keywords: Mono-antibody, breast cancer, trastuzumab, sacituzumab govitecan

1. Introduction

Breast cancer is the second-leading source of death among female cancers and has become the most prevalent cancer in females. According to the "American Cancer Society", American women will eventually get breast cancer. It develops when aberrant cells start to proliferate out of control. These aberrant cells typically develop into tumors that can be recognized as a lump in the breast or seen on the x-ray. The breast may alter in size and shape, may seem lumpy, stiff, or painful if the malignancy is large. Indications include an alteration in pendulous breasts, slight discoloration of the skin, fluids emerging from the breast, and a recently flattened nipple. And clinically, bone discomfort, swollen glands, difficulty in breathing, or pale skin can happen in patients with rapidly spreading disease. In the case of the risk factors, although the actual origin of breast cancer is uncertain, exposure to radiation, a propensity for breast cancer throughout the family and specific genetic alterations contribute to the development [1].

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It can manifest itself in one of two different forms: ductal carcinoma, which occurs in the duct that carries milk to the nipple, or clavicle cancer, which occurs in bundled tissue, or in the mammary glands. Breast cancer also occur in other tissues within the breast, including adipose or connective tissue.

Transplantation, radiation therapy, chemotherapy, hormone therapy, or immunotherapy are all available treatments. For breast cancer in the early stages, surgery is also often performed. Breast cancer that is in its early stages or has progressed to other parts of the body can undergo both radiation and chemotherapy.Usually, "hormone receptor-positive" breast cancer can be treated with hormone therapy and surgical intervention. A cancer therapy called monoclonal antibody therapy uses antibodies to target receptors on cancer cells so that cancer cells are either killed or prevented from proliferating.

According to researchers at "Fred Hutchinson Cancer Research Center, Seattle, WA, USA", monoclonal antibody (mAb) therapy can target and kill cancer cells without harming normal cells. For example, the mAb trastuzumab (herceptin) can be used to treat human epidermal growth receptor 2 (HER2) positive breast cancer [2], which is majorly characterized by the over-expression of the "HER2 protein" upon the surfaces of cancer cells. mAbs are artificial versions of antibodies that are produced in the laboratory. mAbs can also be combined chemotherapy or radiation therapy, to achieve a better efficacy.

Several mAbs including trastuzumab, pertuzumab and ado-trastuzumab emtansine are used to treat breast cancer. For example, mAbs eribulin and trastuzumab were found to be effective to improve the quality of life for estrogen receptor (ER) negative patients and HER-2 positive patients respectively compared to those who received standard chemotherapy. While for PR negative patient, pertuzumab was recommended and for HER-2 negative patients, ado-trastuzumab emtansine was applied. These mAbs are also often combined with other treatments, most frequently the chemotherapy. And it comes with lower recurrence and death rates from breast cancer as well as fewer side effects than chemotherapy alone. Generally, a variety of mAbs are currently being studied and applied for their potential to treat breast cancer. These drugs showed great potential especially in improving metastatic breast cancer (MBC) patients' life quality.

2. Monoclonal antibody drug for cancer

2.1. History and development of mAbs drug therapy

The history of mAb drug therapy began in the 1970s when researchers found a way to massively produce a specific type of antibody in the laboratory. This introduced a possibility of using these antibodies to treat various diseases. The mAb drug was developed in the 1970s when scientists realized that large quantities of a specific type of antibody can be produced in the laboratory [3]. Rituxan (rituximab), which had been authorized by the US "Food and Drug Administration (FDA)" in around 1997 for treating non-lymphoma. Hodgkin's was the inaugural mAb medication. Since then, more mAb drugs have been approved to be applied in various diseases including breast cancer.

Several mAb drugs are being tested in clinical trials aiming at treating breast cancer. Trastuzumab-based medications herceptin, kadcyla, and perjeta are a few of them. The parentheses are explaining that pertuzumab, pertuzumab-trastuzumab, and ado-trastuzumab emtansine are all trastuzumab-based medications. Herceptin is a mAb drug that targets the HER2 protein and is especially effective to treat HER2-positive breast cancers. Kadcyla is also a HER2-targeted mAb drug and combined with chemotherapy when treating "HER2-positive" breast cancers. Perjeta is another one targeting the HER2 protein and is used in combination with herceptin and chemotherapy [4].

2.2. Principles

The principle behind monoclonal antibody drug therapy is to target specific cells or proteins associated with the disease while keeping healthy cells unharmed. This is achieved by creating drugs that bind to and block the function of target cells or proteins. Cancer, autoimmune diseases and infectious diseases can all be treated with monoclonal antibody drugs. By focusing on and hindering the function of lymphocytes invading normal tissues, immunotherapeutic drugs have been used to treat malignancies

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such as breast cancer, autoimmune diseases such as rheumatoid and psoriatic arthritis. Monophane drugs are also used to treat infectious diseases such as hepatitis C, by targeting and destroying the virus that causes the disease.

Another principle behind monoclonal antibody drug therapy is that it can be used to deliver other drugs, such as chemotherapy drugs, directly to target cells or tissues. This is achieved by attaching the drug to the monoclonal antibody drug. This targeted drug delivery allows higher concentrations of the drug to be delivered to target cells or tissues while minimizing exposure to the drug by healthy cells and tissues. This can lead to fewer side effects and more effective treatment [2].

3. Common Mono-antibody in breast cancer

3.1. Sacituzumab govitecan

3.1.1. Mechanism. Suggests that salxituzumab gothakan may be beneficial in the fight against breast cancer. Antibody-drug conjugates (ADCs) target and kill cancer cells that have expressed trop-2, which is found in most breast cancers. The ADC consists of a single antibody and a payload of SN-38 targeting Trop-2, a topoisomerase I inhibitor that can penetrate DNA and cause DNA damage [5], leading to cell cycle slowdown and apoptosis. In preclinical studies, sacitizumab small toxlobulose has been shown effective in trop-2-positive breast cancer cell lines with a semi-inhibitory concentration of 0.3 nM in the MDA-MB-231 cell line.

3.1.2. Clinical data. At least two consecutive treatment regimens failed in one salsaturizumab intervention in patients with MBC and refractory disease, such as anthracyclines and paclitaxane, up to a maximum of 42 patients with salsatuzumab. Side effects include neutropenia (38%), fatigue (35%), and diarrhea (28%). 18% of individuals developed neutropenia at grade 2/4. The combined response rate was 4% and the overall response rate was 28%. The average reaction time was 5.7 months. These findings suggest that salxituzumab govitican is beneficial in patients with "metastatic" complications who have previously experienced treatment. Neutropenia, tiredness, and diarrhea were among the most frequent side effects. And a phase II clinical studies showed that sacituzumab govitecan had an infection prevention rate of 81.0% and an overwhelming response rate of 34.3% in patients suffering from "metastatic triple-negative breast cancer (TNBC)" [1].

Major outcome of the trial was survival. Clinical trials in patients with her2-positive breast cancer who have already received trastuzumab have demonstrated the effectiveness of salsitizumab against vegans [1]. Its common side effects include weakness, constipation, headache, nausea, loss of appetite, dehydration, and exhaustion.

3.2. Trastuzumab

3.2.1. Mechanism. Firstly, binding to targeted HER2 can appeal to cytotoxic, innate immune cells in the tumor microenvironment by trastuzumab's IgG1 Fc region activating natural killer cells' Fc γ RIII/CD16, which is known to as antibody-dependent cell-mediated cytotoxicity (ADCC).

Secondly, its extracellular binding accelerates HER2 degradation via a ubiquitin ligase, c-CBL. Researchers used L26 as an example of the mAb to complete the experiment in mice model. As a result, the tumor growth in mice can't be monitored for over 30 days and the inhibitor causes the lost of HER2 expression gradually [6].

Lastly, the binding of HER2-specific ligands and HER2-receptors causes the formation of homodimers or heterodimers. Thus, certain tyrosine residues in the cytoplasmic domain area are phosphorylated or trans-phosphorylated to activate many intracellular signaling pathways [7]. Therefore, the inhibition of HER2 dimerization has a significant impact on suppressing the HER2-mediated cell signaling and tumor growth. There is a well-accepted way to suppress HER2 activation and Akt phosphorylation by the inhibition of HER2 dimerization [8]. The most well-known method is to inhibit

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the pathways of MAPK and PI3K or Akt, which can suppress the cell growth and proliferation. Researchers demonstrate that the trastuzumab and HER2 receptor binding blocks tyrosine kinase Src signaling, which inhibits PI3K/Akt signaling, cell growth, and survival reduction [9].

3.2.2. Clinical data. Researchers have completed an experiment from 1995 to 1997 with women patients diagnosed with MBC while never treated. Patients were randomly received either chemotherapy alone or chemotherapy plus trastuzumab [10]. Compared to the group with chemotherapy alone, the administrations of chemotherapy plus trastuzumab had significant higher rate with respect to the duration (median of 9.1 vs. 6.1 months; $P<0.001$) and the time until treatment failure (median of 6.9 vs. 4.5 months; $P<0.001$) [14]. Therefore, clinical benefits of trastuzumab is evident in increasing the rate and time of survival.

In addition to MBC, trastuzumab also functions in HER2-positive early breast cancer. When adding trastuzumab into chemotherapy as further therapy, the rate of relapse (reduction of 9.0%), and mortality (reduction of 6.4%) in patients are further decreased by about a third compared with chemotherapy alone in the first ten years of follow-up [11]. There is no remarkable difference between the reductions in recurrence of ER-positive and ER-negative diseases by adding trastuzumab.

The treatment based on trastuzumab is highly effective to lower the rate of recrudesce and death for HER2-positive early breast cancer patients, and increase overall survival of patient staged MBC. Nonetheless, it has several inferior influences on patients' physical health. For example, cardiac dysfunction and cardiac toxicity are the major side effects of trastuzumab, and cases with older age or cardiac comorbidities are linked with higher congestive heart failure (CHF) risk [12]. In addition, study shows that extensive incidence of gastrointestinal toxicities (GIT) including nausea, vomiting, abdominal pain, and diarrhea were introduced by single-agent trastuzumab administrations. And it also induces non-GIT-related toxicities such as respiratory symptoms and fatigue.

3.3. Other novel mono-Ab

Margetuximab is the second-generation anti-HER2 mAb. Compared with trastuzumab, its therapy in the clinical trials increases the progression free survival (PFS) benefit with a relatively 29% risk reduction, acceptable safety and greater maximum cytoxicity against tumor cells [13].

4. Combined application of Mono-antibody drugs

Although more and more mAbs have been assessed in clinical studies and approved for application and marketing, their ability to bind only a single target is not efficient enough to meet the clinical requirements. In this case, ADC is introduced to apply to the treatment as a new therapy. It combines the properties of specific targeting from mAbs and small molecule drugs, which has the potential to improve cancer treatment further more [14]. This category of drug has become one of the most promising and quickest developing fields of cancer therapeutics to cancers in the past few years.

4.1. Combination of trastuzumab and pertuzumab

Pertuzumab is another anti-HER2 humanized mAb that prevents the formation of HER2 dimers, which is complementary to the functions of trastuzumab. Thus, the combination of trastuzumab and pertuzumab can provide a stronger function to block the signaling pathways sufficiently than either agent alone. They enhanced the anti-tumor ability dramatically, promoted regression of tumor and inhibited the metastatic tumor spread compared with single-agent treatments. Clinical trials using combination of pertuzumab, trastuzumab and docetaxel significantly improved independently assessed PFS, which was prolonged 6.1 months compared with the control group [15]. However, the accessed PFS is different in subgroups, such as patients who have treated with trastuzumab and patients with hormone receptor-positive MBC. The incidences of adverse events and side effects of the combination tend to have a higher percentage of occurrence than in the control group but were generally balanced in the two groups [15].

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4.2. Anthracycline – trastuzumab emtansine

Trastuzumab emtansine (T-DM1) is an ADC that is broadly practical to treat the advanced breast cancer. Trastuzumab can inhibit the signaling of HER2 and mediate ADCC. Active DM1 metabolites can destroy the microtubule network, causing damage to transportation in cells and death, which is the basic mechanism of T-DM1. T-DM1 shows superior activity compared with trastuzumab on trastuzumab-sensitive breast cancer cell cultures and tumor xenografts, which presents great value to the application [16]. Moreover, trastuzumab is potent to increase the PFS and lifespan with less incidences of adverse events for patients with advanced breast cancer and MBC.

4.3. Taxane-trastuzumab

A reversible small molecule tyrosine kinase inhibitor, lapatinib, targets the HER2 intracellular kinase domain.It was demonstrated that the apoptosis and tumor control are improved by the conjugate of lapatinib and trastuzumab in HER2-positive xenografts, and it causes a marked accumulation of inactive HER2 on the cell surface in conjunction with enhanced cytotoxicity [17, 18]. The researchers have observed the drug interaction on the tumor in the groups of HER-2-overexpressing cell lines. Compared to the treatment with lapatinib alone, the PFS has increased dramatically and OS was achieved in the combination group. Furthermore, this combination is also beneficial in the neoadjuvant environment.

5. Future outlook & limitation

Despite the promising results of mAb therapy, there are still limitations. Except the toxic and side effects which is discussed partly above, there are others worth mentioning. To illustrate specifically, mAb can be expensive for cases in developing countries so that is difficult to get prevalence worldwide. It only works in the patients with a positive molecular target. Additionally, mAb therapy is not suitable for all classes of breast cancer. For example, the ER-positive one, which takes up 70% of cases is more generally beneficial with the therapy of hormone agonists in combination with a standard adjuvant [19].

With the quick development of medicine, different types of breast cancer find latest resolution in the areas of monoclonal drugs. For example, the researchers developed the novel Trop2-directed ADC, datopotamab deruxtecan (Dato-DXd, DS-1062a), with a potent DNA topoisomerase I inhibitor (DXd) [20]. In the evaluation of pre-clinical models and animal models, it showed effective anti-tumor activity with tumor regression and acceptable safety, which is encouraging especially for patients diagnosed with TNBC [20, 21]. Moreover, in the randomized clinical trials composed of 900 patients, the cases with metastatic TNBC both in the intention-to-treat population and the PD-L1-positive subgroup demonstrate prolonged PFS with the treatment of atezolizumab plus nab-paclitaxel [22]. On the other hand, trastuzumab deruxtecan, an ADC, has been conducted in the clinical trial to investigate its ability to control disease, to bring clinical benefit, to sustain response and to create progression-free survival. The result showed relatively sustained anti-tumor effectiveness in a pre-treated population with HER2-positive MBC [23]. In the case of cost, a subcutaneous formulation emerged as the newly developed injection method of mAbs with comparable effects and safety profiles since 2013. It received preference from the patients because it does not need pharmacy preparation and has a shorter administration time, specific to 1500 hours reduction of total time and 1-2 facility infrastructure releases per day. Furthermore, the overall efficacy of subcutaneous formulation is not inferior to intravenous injection. In this way, the saving of clinical resources may resolve the cost problem of mAbs and improve total medical care.

6. Conclusion

In conclusion, the history and development of mAb, specific examples with mechanism and clinical efficacy, its combination therapy and newly developed tendency are introduced and summarized. The exploitation and follow-up development of mAb have drastically improved the treatment and prognosis of HER2 positive and other types of breast cancers. For example, TNBC which is generally more serious than other types also ushers its new springtime for healing because the presence of mAb. Many researchers believe that mAb therapy will become new standard for treating breast cancers. For instance, “American Society of Clinical Oncology” has issued guidelines recommending mAb therapy

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in the treatment of HER2-positive breast cancer. Moreover, the "National Comprehensive Cancer Network" has issued guidelines recommending mAb therapy in the treatment of MBC. Despite the limitations of cardiotoxicity and diarrhea and so on, mAb therapy is a promising treatment option for breast cancers since its first approval by the FDA in 2006. In the future, mAb therapy is expected to play an increasingly important part in treating breast cancer. Novel mAbs with higher efficiency are being studied and also aiming to lower the side effect of mAb as far as possible.

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