

Progress in immune-drugs of Hemato-oncology

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Abstract. Hematological tumors are a significant disease that poses a serious threat to human health, with morbidity and mortality rates ranking among the highest for all types of tumors. Targeted and immunotherapy for hematological tumors have made significant progress in various aspects, and the utilization of new drugs has enhanced the overall effectiveness of treating hematological tumors. As medicine enters a new era of personalized treatment, monoclonal antibody drugs, with their unique mechanism of action and high efficiency, play an immeasurably important role in the treatment of malignant tumors. Monoclonal antibodies are also utilized as targeting agents for delivering nanomedicines containing cytotoxic payloads or directly linked to cytotoxic drugs. The use of monoclonal antibodies has become a popular treatment for hematologic tumors, as evidenced by significant commercial success. The main features of monoclonal antibody drugs compared to traditional chemical drugs are that monoclonal antibodies are biological drugs with higher biotransformation efficiency, i.e., a higher success rate, and fewer side effects. However, targeted drug monotherapy often yields poor remission rates, and the efficacy and safety of immunotherapy need further enhancement. This article will begin by discussing hematological oncology and provide an overview of the principles, advantages, and disadvantages of several common monoclonal antibody drugs currently available on the market. It will also explore the potential for combined use of monoclonal antibodies, offering direction and assistance for future research in this field.

Keywords: Hematologic tumor, Monoclonal antibody, Antibody development.

1. Introduction

Hematological system tumors are common malignant tumors with the highest morbidity and mortality rates, and are malignant diseases that seriously affect human health [1]. Hematological malignancies include a series of heterogeneous diseases, all originating from cells of the bone marrow and the lymphatic system, and are divided into three main categories: leukemias, lymphomas and plasma cell tumors. Its main manifestation for the blood system, malignant cell proliferation manifestations [2], such as acute leukemia, manifested as abnormal proliferation of malignant leukemia cells in the bone marrow, resulting in the inhibition of normal hematopoiesis in the bone marrow, which in turn causes severe anemia, thrombocytopenia caused by hemorrhage, the occurrence of infections. At the same time, many leukemia cells in bone marrow proliferate and release to peripheral blood, and then circulate to various organs and organs in the whole body with blood circulation, causing the involvement of many organs such as central nervous system, bones, joints, lungs and even the heart, which seriously affects the function of organs. Lymphoma is a type of malignant tumor originating from lymphatic tissues and includes two major types, Hodgkin's lymphoma, and non-Hodgkin's lymphoma (NHL). Lymphoma can invade any part of the body and has a variety of clinical manifestations, usually characterized by enlarged lymph nodes, fever, lethargy, and night sweats. And plasmacytomas are systemic tumors that originate in the bone marrow and eventually involve most of the bones of the body, especially in adult life where there is red bone marrow. Plasmacytomas may present as a single lesion (isolated plasmacytoma) or multiple lesions, known as multiple myeloma. Isolated plasmacytomas most commonly occur in bone (osteoplasmytoma) but can also be seen in extraosseous soft tissues (extramedullary plasmacytoma); Isolated bone plasmacytomas are confined bone tumors consisting of a single clone of plasma cells without the other features of multiple myeloma, such as anemia, hypercalcemia, impaired renal function, or multiple osteolytic lesions, while multiple myeloma produces monoclonal immunoglobulins that invade and destroy adjacent bone tissue [1,2,3].

Multiple primary malignancies have been reported in approximately 17% of all cancer events reported annually by the National Cancer Institute in the USA, with the incidence of multiple malignancies in patients with leukemia and non-Hodgkin's lymphoma being 7.2% and 7.7%, respectively. The incidence of multiple malignancies in patients with multiple bone marrow tumors is slightly lower (5.6%) than in patients with multiple bone marrow tumors [4]. In one study, the slightly lower incidence of multiple malignancies, with only 2.3% of patients developing a second malignancy, may be related to the fact that the study population consisted of patients with hematological neoplasms, and that the risk of acute leukemia was significantly increased after non-Hodgkin's lymphoma compared with the general population [4]. Chronic lymphocytic leukemia is a common type of leukemia in Western countries. The American Oncology Association estimates that there will be 20,000 new cases of CLL and about 4,400 deaths in the U.S. in 2022; most of the cases and almost all the deaths will be in adults. The average age of patients with CLL is 70 years. CLL is extremely rare in children.

In the face of these cancers, today's modern medicine allows for personalized and specific treatments based on an individual's particular disease characteristics. Advances in knowledge of immunology, molecular biology and biochemistry have made monoclonal antibodies a model for personalized therapy. A single B-cell clone can create highly homogenous antibodies called monoclonal antibodies, which are only directed against one antigenic epitope. Orthoclone OKT3 (muromonab-CD3) was the first licensed monoclonal antibody, approved in 1986 for the purpose of avoiding rejection of kidney transplant recipients. However, the side effects were relatively large, and it was only used in acute cases at the time. Since the approval of ipilimumab, the first immune checkpoint inhibitor, an anti-CTLA-4 monoclonal antibody, it has been found in clinical trials to be more effective than conventional drugs [5]. As a result, in recent years enthusiasm for cancer immunology research has shifted to the study of the formation of the immunosuppressive environment, the mechanisms of immunosuppression in cancer tissues, and the molecules and cells involved in these pathways.

The discovery and refinement of hybridoma technology in 1975 produced the monoclonal antibody initially, which was fully licensed in 1986, and then the first humanized antibody drug was approved in the U.S. in 1997. The maturation of phage display technology in the meantime has also laid the foundation to produce fully human antibody drugs, which can be produced much faster than traditional hybridization techniques. The development of antibodies offers a novel strategy that can target certain mutations and flaws in the production and structure of proteins in a variety of illnesses and ailments [5]. As gene sequencing technology advances and fundamental medical research is used in clinical settings, humanized monoclonal antibodies are emerging as the biotechnology molecule-derived product category with the quickest rate of growth. About 30 monoclonal antibodies are currently approved by the U.S. Food and Drug Administration (FDA) approves the use of various drugs and treatments for human use.

2. Principles of Monoclonal Antibodies

The function of any compound molecule is determined by its structure and monoclonal antibodies are no exception. A monoclonal antibody consists of a "Y"-shaped structure composed of an antigen-binding site (Fab) and a crystallizable site (Fc), with the Fab being responsible for recognizing the bound antigenic target, which determines the specificity and affinity of the monoclonal antibody, while the Fc binds to the Fc receptor, which is expressed on the surface of the immune effector cells, as well as to the complement and scavenger receptor (FcRn), which determines the specificity of the antibody and the affinity of the monoclonal antibody. FcRn), which determines the immunologic effect of the monoclonal antibody and its half-life in the body. Based on these two structural features, monoclonal antibodies can be roughly categorized into two mechanisms of action related to Fab and Fc, as well as further subdivisions underneath. In addition to this, monoclonal antibodies can elicit acquired immunoprotection, including activation of cellular immunity such as tumor antigen-specific

cytotoxic T cells and helper T cells, and humoral immunity such as protective antibodies against tumor antigens. Studies have shown that rituximab is effective against lymphoma and has low toxicity; it has also shown significant efficacy against chronic lymphocytic leukemia (CLL) [6]. Alemtuzumab (anti-CD52) has shown efficacy in patients with previously untreated or refractory CLL [7]. And gituzumab ozogamicin (anti-CD33) has shown significant efficacy in acute myeloid leukemia [8]. These monoclonal antibodies kill tumor cells through complement-mediated cytotoxicity, antibody-mediated cytotoxicity, and induction of apoptosis [5,6,9].

3. Application of Monoclonal Antibodies

3.1. Rituximab

The development of autoimmune diseases is greatly influenced by the role played by B cells. During the differentiation of pre-B cells to mature lymphocytes, CD20 is expressed on the surface and is responsible for the regulation of B-cell growth and differentiation. Rituximab is the distinction of being the first monoclonal antibody approved for the treatment of cancer [5]. As a chimeric monoclonal antibody, rituximab targets CD20, a protein located on the surface of B lymphocytes. The expression of CD20 molecule is abnormally high in B-cell lymphoma, non-Hodgkin's lymphoma, and multiple myeloma, and CD20 is not expressed in hematopoietic stem cells, progenitor cells, normal plasma cells, and other normal tissues of the human body [6]. Therefore, anti-CD20 can be a good therapeutic target for the treatment of B-lymphoblastic tumors. This targeting has significantly altered the management of B-cell non-Hodgkin lymphomas (NHL), chronic lymphocytic leukemia (CLL), and has been instrumental in the treatment of rheumatoid arthritis (RA) and other autoimmune diseases [5,6]. When it comes to autoimmune diseases like RA, rituximab has been particularly effective for patients who have not had success with tumor necrosis factor (TNF) inhibitors, offering them a new lease on life by reducing symptoms and decelerating disease progression. A cohort study showed that patients receiving medication for lymphoma were 2.70 times more likely to achieve a complete remission after treatment compared to those receiving medication for RA. In addition, since 2002, multiple case reports and retrospective studies have confirmed the efficacy of rituximab for pemphigus vulgaris. The rate of complete remission has varied from 47% to 89.5%, while relapse rates have varied from 18% to 52% [6].

A study conducted on 126 lymphoma patients treated with anti-CD20 drugs found that 55 percent of them had an antibody response to the COVID-19 vaccine [5]. Although there are no definitive criteria regarding rituximab versus COVID-19 vaccination, COVID-19 vaccination during rituximab therapy is not recommended at this time.

Infusion reactions during the first treatment with rituximab are the most common adverse reactions, but they can be prevented or mitigated with medications such as corticosteroids, acetaminophen, or diphenhydramine. Moreover, rituximab has also been associated with reactivation of a variety of viruses, including, but not limited to, hepatitis B virus and JC virus, so care needs to be taken in checking the patient's condition when using rituximab [6]. Serious or even fatal adverse reactions have occasionally occurred with rituximab, but they are extremely rare [6]. Overall, rituximab is a safe and well-tolerated monoclonal antibody.

3.2. Alemtuzumab

CD52 is widely distributed on the surface of normal B and T lymphocytes and their surfaces, monocytes, and macrophages, and is particularly abundant on the surface of chronic lymphocytic leukemia cells [7]. A unique mechanism of action is present in alemtuzumab, which has been shown to be highly effective in the treatment of a variety of malignant tumors of B- and T-cell origin, such as NHL, CLL, T-ALL, and acute myeloid leukemia (AML) with FLT3-ITD mutation in the presence of CD52-expressing diseases. Alemtuzumab was marketed in Europe and the United States as early as 2001 for the treatment of patients with fludarabine-refractory chronic lymphocytic leukemia (CLL) [7].

Alemtuzumab was most effective in hematologic, splenic, and myeloid CLL, but less effective in lymph node disease. The feasibility of alejumab as consolidation therapy to eliminate minimal residual disease was first demonstrated in 1997 [7]. In many previous studies, drugs were administered intravenously, but infusion toxicity was observed in many patients. Subcutaneous administration became more popular when it was found to achieve the same blood levels as IV administration, although it took longer, but with less subsequent toxicity. However, this drug is not approved for consolidation therapy [10]. Preliminary safety data from the U.S. clinical CALGB10101 trial showed that 6 of 51 patients treated with alemtuzumab as consolidation therapy after three chemotherapies died of infections, suggesting an increased risk of infection-related complications.

3.3. Ofatumumab

Ofatumumab is a fully humanized CD20-targeting monoclonal antibody used in refractory chronic lymphocytic leukemia (CLL) that is refractory to fludarabine and alemtuzumab. This monoclonal antibody specifically kills B-lymphoma cells through targeted binding to the small ring antigen on small and large CD20 molecules, which leads to cytolysis and specifically induces apoptosis of CD20 cells, with no adverse effects on other normal tissues [11]. In addition, the rate of CD20 shutdown by otumumab is lower than that of rituximab, which would result in greater activity, especially when CD20 expression levels are low [12]. And in one study, otolimumab improved and prolonged survival (60% by the end of the study) and inhibited tumor growth. In contrast, in the same xenograft model, rituximab also inhibited tumor growth and prolonged survival during the study period, although it did not show a significant survival prolongation effect by the end of the study [11]. The study demonstrated that otuzumab had a significant dose-effect relationship, while rituximab only resulted in a slight extension of survival at the highest doses [11].

Ofatumumab has a pregnancy grade C and does not require dose adjustment in patients with renal impairment. Ofatumumab was approved by the U.S. FDA under the accelerated approval process on October 26, 2009 and is manufactured by GlaxoSmithKline under the trade name Arzerra [13].

In a clinical trial, fludarabine and alemtuzumab were shown to be difficult to treat, and treatment with otolumab resulted in an overall efficiency of 42%, with a median response time of 6.5 months. The complete remission rate was 32% in the 500mg dose group and 50% in the 1000mg group; the overall response rate was 77% in the 500mg dose group and 73% in the 1000mg group. There were no unexpected adverse events in the trial, which is a positive result for the product as a first-line drug [13].

3.4. Gituzumab

Gituzumab is a humanized monoclonal IgG4 antibody coupled to the deoxyribonucleic acid (DNA) embedding agent calicheamicin (CLM). CD33 antigen is expressed on the surface of leukemic cell debris in more than 90% of patients with acute myelogenous leukemia (AML) [14]. CD33 is a transmembrane glycoprotein specifically expressed on the surface of myeloid leukemia cells and acts as a sialic acid-dependent cellular adhesion molecule, mediating intermolecular interactions in the sialic acid environment to regulate the proliferation and differentiation of target cells. One in vitro study demonstrated that gituzumab-induced cytotoxicity was positively correlated with the level of CD33 expression; the higher the level of CD33 expression, the stronger the binding of gituzumab to the CD33 antigenic site, thus enhancing clearance of AML cells. In 16% of adults with acute myeloid leukemia who had a first relapse, treatment with it led to complete remission, and in 13% of patients, complete remission but incomplete platelet recovery after treatment with gituzumab ozogamicin. There was no difference in remission rates between patients younger than 60 years of age and those older than 60 years of age [14]. In clinical trials of gituzumab ozogamicin, Myelosuppression and elevated liver enzyme levels are the most frequent adverse effects. Mucositis, neuropathy, and liver and kidney dysfunction are just some of the significant adverse effects that conventional chemotherapy can cause, in addition to severe bone marrow suppression [14]. The FDA officially approved the use of Gituzumab in May 2000 for the treatment of patients over 60 years old who have

their first relapse of AML and have CD33 positivity who were not suitable for chemotherapy, but subsequently withdrew the drug from the market in 2010 due to certain safety concerns. After adjusting the dosage and conducting many clinical trials, the benefit-risk ratio of the drug was finally recognized, and the FDA re-approved gituzumab for patients with first-time and relapsed refractory CD33-positive AML in 2017.

Evidence of severe hepatic injury was observed in two patients in one study (one with hepatic failure and one with persistent ascites and hepatosplenomegaly). On a brighter note, however, treatment-related cardiotoxicity, renal failure, and oral celiac disease were not reported [8]. In an evaluation of a phase I study, gituzumab-ozogamicin, some adverse reactions were seen, although no treatment-related toxicity was also observed in terms of central nervous system, cardiac, or renal function [8]. Gituzumab-ozogamicin is currently relatively well tolerated; the incidence of mucositis is low, despite this, the drug is not recommended for patients who have hepatic insufficiency.

3.5. Combination with Drugs

Combining rituximab with other therapeutic drugs and treatment modalities is advantageous because it can increase tumor cell sensitivity to chemotherapy. Especially for elderly patients who are unable to tolerate high doses, the combination of rituximab and prednisolone is highly effective [9]. The 2-year survival rate for the combination was 70%, compared with 59% for prednisolone alone [15]. Alemtuzumab in combination with rituximab with the aim of increasing its complete remission (CR) and eliminating minimal residual disease [7]. Patients with relapsed lymphoma were treated by scientists with alemtuzumab and rituximab, and achieved a response rate of 52%, with 8% being in complete remission. This indicates that the combination of alemtuzumab and rituximab is both safe and viable [9]. However, hypotension, fever, nausea, headache, vomiting, shortness of breath, bronchospasm, chills, fatigue, rash, dyspnea, diarrhea, and infection are all common complications reported in clinical studies. Although the combination was well tolerated, 27% of patients (13 of 48) in one study developed Cytomegalovirus antigenemia, 15% of which was related to infection and required treatment [7].

4. Conclusion

With the development of biotechnology and medicine, monoclonal antibody therapy has made significant progress in the treatment of hematologic tumors. By targeting the immune system is activated to attack tumor cells by specific antigens on their surface, monotherapy can provide more individualized and effective treatment. In the future, with the in-depth study of tumor molecular biology and immune regulation mechanism, it is expected to develop more monoclonal antibody drugs with targeting, less toxic side effects, and more adapted to different blood tumor types. At the same time, the exploration of the combined application of monoclonal antibody therapy with other therapeutic means (e.g., chemotherapy, radiotherapy, immunotherapy, etc.), as well as the development of personalized therapeutic protocols, will lead to improved efficacy, fewer side effects, and better therapeutic outcomes for patients. It is worth mentioning that the consolidation therapy of alanzumab, especially for AML, After AML induction therapy, high-dose consolidation and intensive therapy are crucial for achieving CR in the follow-up treatment of AML, which largely determines the duration of remission, survival, and time to relapse of AML. In other words, after the CR if not further consolidation, intensive therapy, almost 100 percent of the sooner or later will be relapsed. so, CR should be given as soon as possible to consolidate the consolidation of intensive therapy.

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