The Current studies of Monoclonal Antibody Drugs in Lung Cancer, Breast Cancer, Leukemia and Lymphomas

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Abstract: Nowadays, Cancer is a focus of concern in immunology research because the effect of existing therapies is very limited. However, monoclonal antibodies have excellent curative effects because of their working mechanism always along with high target-specificity. A clear arrangement is needed on the effective mode of monoclonal antibody drug products in the treatment of different cancers. In this review, we introduced the history of the discovery and developments of mAbs. Besides, the molecular structure, mechanism of action, and classification of mAbs were well illustrated. In addition, we elaborated on the applications of mAbs against lung cancer, breast cancer, leukemia, and lymphatic carcinoma. Overall, mAb is a mighty discovery. In the future, as more reaction mechanisms involved with antigen-antibody binding are studied, the application range of monoclonal antibodies will be more extensive. Therefore, mAb has great potential to solve medical problems.

1. Introduction

Cancer ranks as a leading cause of death in the world today. According to statistics from the World Health Organization (WHO) in 2020, cancer is the second leading cause of death. Currently, one-in-five people worldwide will develop cancer in their lifetime, and one-in-eight men and one-in-eleven women will die from it[1]. Cancer is a malignant tumor of potentially unlimited growth that expands locally by invasion and systemically by metastasis, thus difficult to cure. The advent of immunotherapy, however, has brought hope for cancer treatment.

Cancer immunotherapy is one of the hottest fields in cancer research today. It not only represents a radical breakthrough in the basic biology of cancer, but also has achieved astonishing therapeutic results in clinical practice. Cancer immunotherapy can be divided into five types: adoptive T cell therapy, immunomodulator, tumor vaccine, targeted antibody and oncolytic virus. Among them, targeted anticancer therapy is to use specific drugs to specifically inhibit the specific oncoproteins and related tumor growth factors expressed only in tumor tissues and cells, so as to kill cancer cells while not affecting other normal cells. Although most people think of small molecule inhibitors that can be absorbed by oral administration and can spread across cell membranes into cells as targeted drugs, the most effective targeted anticancer drugs so far are large molecule monoclonal antibodies (mAbs).

MAbs are highly homogeneous antibodies that are produced by cloning a single B cell and are specific to a specific epitope. MAbs have been considered to be of great value in the diagnosis and treatment of human cancer because they can combine with tumors to achieve indirect therapeutic effects, thus widely used in clinical treatment of tumor at present.

Back in 1890, physiologist Emil von Behring and microbiologist Shibasaburo Kitasato discovered antibodies, which are protective toxins from exposure to diphtheria or tetanus toxins in the blood of

animals. Then in the early 1900s, an immunologist Paul Ehrlich put forward a hypothesis of a compound which can selectively target disease-causing organism and deliver toxins to that organism. Ehrlich and Élie Metchnikoff received the 1908 Nobel Prize in Physiology or Medicine for the discovery of phagocytosis. Their work laid the theoretical foundation for immunology.

Until 1975, George Köhler and Cesar Milstein described the production of specific monoclonal antibodies, each produced by a continuously growing cell line which is created by immunizing mice with cells that produce antibodies and combining them with immortal cancer cells that produce antibodies [2]. This discovery has led to important biological discoveries and clinical applications in the treatment of autoimmunity and cancer.

In 1988, Greg Winter's team pioneered the technology of humanized monoclonal antibodies, which eliminated many of the immune rejection reactions caused by monoclonal antibodies in patients.[3] By the 1990s, research about mAbs in immunotherapy had made great progress.

Currently in medicine, monoclonal antibodies have an increasingly important role. In addition to their impact on medical diagnosis, the therapeutic use of antibodies has led to remarkable successes in the treatment of autoimmune diseases and cancer. The 2018 Nobel Prize in Physiology or Medicine was awarded for "the discovery of cancer therapy through antibody mediated inhibition of negative immune regulation".[4] As often happens in biology, the mechanisms and effective induction of the inhibitory process on which this type of immunotherapy is based remain unclear, providing new challenges to ongoing research and new perspectives that are driving the development of monoclonal antibodies against other targets. Therefore, we review recent researches in the classification, mechanism and application of mAbs.

2. Classification of mAbs

There are four types of mAbs, murine, chimeric, humanize and human. The first monoclonal antibody to be discovered and replicated was a murine monoclonal antibody. This type of mAb is derived from collecting B lymphocytes from the mouse spleen and then fusing it with an immortal myeloma cell line lacking the hypoxanthine-guanine-phosphoribosyltransferase (HPTR) gene. All these mAbs are identified with names ending in -omab (i.e., muromonab-CD3, blinatumomab, capromab). Allergic reactions are common in the human body and usually result in the production of anti-drug antibodies. Because of the relatively weak binding to human FcRn, murine mAbs also showed a short half-life when used in humans. For oncology, these mAbs may not be the most beneficial which is caused by the "relatively poor recruiters of effector function, antibody-dependent cytotoxicity, and complement-dependent cytotoxicity", which are required for tumor destruction basic skills.[5] The chimeric mAb uses murine antigen-specific variable regions, but the remaining heavy and light chains are human. This was done using genetic engineering techniques, which produced approximately 65% of human and 35% of murine mAbs. The names of chimeric mAbs end with -ximab (i.e., rituximab, infliximab, cetuximab). Compared with their mouse counterparts, these monoclonal antibodies "show a longer half-life in the human body and show reduced immunogenicity, but despite this, the tendency of chimeric monoclonal antibodies to induce anti-drug antibodies is still considerable. Considerable."[6] Humanized mAbs are created by rasterizing the hypervariable regions of mouse light and heavy chains onto a human antibody framework. This results in about 95% of the molecules being human. This leads to a reduction in the production of anti-drug antibodies. However, the process of creating these molecules is arduous and has limitations. The names of these mAbs end in -zumab (ie trastuzumab, alemtuzumab, bevacizumab).[7] With the development of new technologies, fully humanized monoclonal antibodies can be created. These are created using animals that carry human Ig genes. These transgenes include part of the variable region, allowing human antibodies to recombine. The animal's own endogenous Ig gene has been inactivated, so that a completely human mAb can be produced. Compared with other types of mAbs, these mAbs are less antigenic and better tolerated. In addition, compared with other categories, they still seem to be present in the circulation of the human body. The names of these mAbs end with -umab (ie ofatumumab, daratumumab, denosumab).[8]

There are three types of mAbs, depending on how they are administered or used: unconjugated, conjugate and bispecific monoclonal antibody. Unconjugated mAbs or

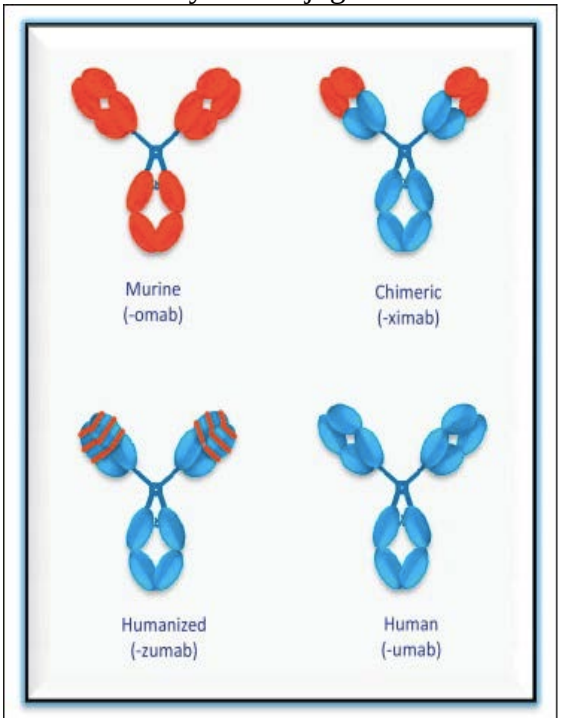

Figure 1. Classification of mAbs. (https://docplayer.fr/61010399-Principes-de-production-et-d-utilisation-des-anticorps-monoclonaux.html)

"naked" mAbs are antibodies which act on their own. They are the most commonly used methods of the cancer treatment. In most cases, the antigens of these molecular will attach on cancer cells, which may enhance people's natural immune response to cancer cells. Meanwhile, mAb attracts immune cells and helps to enhance the immune system's recognition of cancer cells, thereby increasing cell apoptosis. Another mechanism is to target immune system checkpoints, and other unbound mAbs block antigens on cancers which helps them expand and proliferate. A conjugated monoclonal antibody is defined as the mAb combined with a chemotherapeutic drug or radioactive particles. As the delivery mechanism of chemotherapy or radioactive particles, mAb circulates in the patient's body until the expected target antigen is found. This method helps to minimize damage to normal cells caused by chemotherapeutic drugs or radioactive particles attached to mAbs. Bispecific mAb, a unique type of mAb, is a combination of two different mAbs, allowing the mAb to connect to two different antigens at the same time. One target is the protein found on cancer cells, and the other target is the protein found on immune cells. This combination allows immune cells and cancer cells to be combined to stimulate an enhanced immune response and destroy cancer cells.

3. Mechanism of mAbs

When using mAbs in oncology, there are multiple mechanisms of action that destroy cancer cells. These mechanisms include preventing tumor cell survival cascades, inhibiting tumor growth by interfering with tumor angiogenesis, evading programmed cell death, and evading immune checkpoints.[9]

Depending upon which antigen is bound to the antibody and the Fc region, an antibody-dependent cell cytotoxicity or complement-system cytotoxicity can be generated. This can result in the blocking of cell membrane receptors and inhibiting intracellular signals. Generally, there are two types of monoclonal antibodies: Directing tumor killer and Immune-mediated tumor cell killer. Some monoclonal antibodies are immunotherapy because they help turn the immune system against cancer. For example, some monoclonal antibodies mark cancer cells so that the immune system will better

recognize and destroy them. An example is a rituximab, which binds to a protein called CD20 on B cells and some types of cancer cells, causing the immune system to kill them. B cells are a type of white blood cell. Other monoclonal antibodies bring T cells close to cancer cells, helping the immune cells kill the cancer cells. An example is a blinatumomab, which binds to both CD19, a protein found on the surface of leukemia cells, and CD3, a protein on the surface of T cells. This process helps the T cells get close enough to the leukemia cells to respond to and kill them. In the first condition, the Fab is the part which is responsible for the targeting of the cancer cell, then the Fc binds to the B cells. In the other condition, the Fc was firstly activated to bind and activate the T cell and bring it close to the cancer cell.

4. Application of mAb Technology

4.1 Lung Cancer

The incidence and mortality of lung cancer rank first among malignant tumors in the world. Although surgery, chemotherapy, radiotherapy and the application of molecular targeted drugs have provided the means for the treatment of lung cancer, the prognosis of lung cancer patients is still not optimistic. The interaction between tumor cells and immune system plays an important role in tumorigenesis and immune escape is one of the important pathogeneses of tumor. With the further study of immune response mechanism, tumor immunotherapy has gradually developed from the initial non-specific immunotherapy to specific target-based immunotargeted therapy. Immunotherapy has become an important research area of tumor therapy including lung cancer.

Ipilimumab is a humanized monoclonal antibody targeting CTLA-4. A randomized, double-blind, multicenter Phase ii trial of Ipilimumab combined with paclitaxel/carboplatin in first-line treatment of stage iii B / iv NSCLC enrolled 204 patients. Randomized into 3 groups: placebo control group (6 cycles of carboplatin+paclitaxel+placebo), synchronous Ipilimumab group (the first 4 cycles of carboplatin+paclitaxel+Ipilimumab), Ipilimumab was changed to placebo for the last 2 cycles), CP sequential Ipilimumab group (carboplatin + paclitaxel + placebo for the first 2 cycles, and Ipilimumab was changed to placebo for the last 4 cycles), and Ipilimumab or placebo was given again every 12 weeks as maintenance treatment for patients with therapeutic effect. The results showed that the immune-related disease-free progression time and PFS of CP sequential Ipilimumab group were better than those of placebo control group, and there was no significant difference in PFS between synchronous Ipilimumab group and placebo control group. Based on these data, a phase iii trial (NCT01285609) of 920 patients is currently underway to further evaluate Ipilimumab in lung squamous cell carcinoma.

4.2 Breast Cancer

The human epidermal growth factor (EGF) receptor (HER; erbB) family is a receptor with tyrosine kinase activity, which is expressed in various tumors. At the same time, HER2 as a ligand orphan receptor overexpresses in 25-30% of breast cancers.[10] The vascular endothelial growth factor (VEGF) receptor has also become a target for breast cancer treatment which is caused by angiogenesis playing an important role in tumor growth and metastasis.[11] In this case, antibodies against the extracellular domain of erbBs and VEGF are the main topics of this review.

4.2.1 The Epidermal Growth Factor Receptor Family

The expression of EGFR and HER2 is negatively correlated with estrogen receptor (ER) status, and EGFR-HER2 heterodimers have been shown to increase the metastatic potential of breast cancer cell lines. The overexpression rate of EGFR in TNBC is particularly high, and the negative effect of EGFR overexpression is particularly obvious in TNBC. Therefore, EGFR has the potential as a therapeutic target for TNBC; however, there is currently no specific targeted therapy.

In clinical trials, both trastuzumab and pertuzumab are mAbs against HER2. Trastuzumab is an IgG1 recombinant humanized mAb targeting the extracellular domain of HER2 (p185), developed to eliminate HER2 transmembrane signaling to associate intracellular molecules.[12] Normally,

trastuzumab is used in the treatment of the early stage and advanced breast cancer. On the other hand, resistance of trastuzumab after first one- year treatment is significant.[13] In such a case, trastuzumab use combined with other drug is essential to reduce the trastuzumab resistance,[14] such trastuzumab treatment with taxanes or capecitabine which presents an anti-tumor activity of trastuzumab resistance [15]. Also, CD8+ T cell-eliciting can be used as a combination immunotherapy strategy with trastuzumab to stimulates an immunologic response.[16] Compared with trastuzumab, pertuzumab, another mAb related drug, binds to different epitopes with the HER2 dimerization domain [17], and could significantly activate the NK cell (~75%) *in vitro*.[18]

4.2.2 The Vascular Endothelial Growth Factor (VEGF) Family

The VEGF family consists of six growth factors (VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placental growth factor) and three receptors, VEGFR-1 (Flt-1), VEGFR- 2 (KDR/Flk-1) and VEGFR-3 (Flt-4). Activation of VEGFR-2 by its ligand leads to increased permeability of the vascular system and increased endothelial cell migration and proliferation, making it the main target of treatment.

Due to the high expression of VEGF, the vasculature in the tumor is disordered and abnormal. By neutralizing local VEGF, anti-VEGF drugs can induce the normalization of these blood vessels, leading to a potential decrease in vessel volume and interstitial fluid pressure within the tumor, thereby enhancing the delivery of oxygen and cytotoxic therapy to the tumor.[19]

Currently, bevacizumab, ramucirumab and aflibercept are the effective and approved anti-VEGF breast cancer treatment.[20] Bevacizumab has currently illustrated the advance of the detectable response rates and progression-free survival advantage.[21] By contrast, Bevacizumab have not demonstrated any clinical use in breast cancer.

4.3 mAbs in leukemia

It is wide known that leukemia is a major disease with a high mortality rate, a great threat to human health, and a heavy burden on both families and society. Traditionally speaking, allogeneic bone marrow transplantation is an important therapeutic method. However, the limitations of traditional therapy are noticeable. There are several factors to consider that bring difficulties for the specific implementation of bone marrow transplantation. Matching of donor and recipient for bone marrow transplantation is very restricted due to the need to consider postoperative immune rejection. In addition, the surgical procedure requires total body irradiation as preoperative treatment. So for the elderly, as well as other individuals with poor physical condition, the feasibility of surgery will be greatly reduced. Besides, the personal economic situation is also a factor to be considered. It is obvious that the cost of surgery is a great burden for most families around the world. Therefore, the development of more advanced therapies is of great significance. And fortunately, several monoclonal antibody drugs have significant effects in the treatment of leukemia.

4.3.1 Inotuzumab ozogamicin

B-cell acute lymphoblastic leukemia (ALL) is the most common type of leukemia in pediatric patients, accounting for approximately 80% of patients. The treatment of leukemia in pediatric individuals is quite difficult considering the physical condition of the patients.[22] The situation is often more unfavorable in adult patients. After intervention and symptom relief, disease recurrence with concomitant chemical resistance to drugs often occurs in adult diseased individuals.[23] It is very inspiring that 80% of inotuzumab-treated B-ALL patients could be able to get a complete remission state.[22] Similar to other monoclonal antibody drugs, Inotuzumab ozogamicin (InO) takes advantage of the high specific targeting of monoclonal antibodies. The drug consists of two parts inotuzumab and ozogamicin. Inotuzumab ozogamicin is a humanized antibody-cytotoxin conjugate medication.[24] As a monoclonal antibody, inotuzumab provides targeting to CD22 molecules and undertakes the function of drug targeted delivery. And the ozogamicin is a cytotoxic agent from the class of calicheamicins, which can enter the nuclear of targeted cell and induce the double-strand DNA breakdown.[23] The correct selection of the target molecule is an important factor for the success of

clinical trials of this drug. One of the advantages is the limitations of the CD22 molecule. It is well-known that CD22 is expressed in most (60-90%) precursor cells of B-cell acute lymphoblastic leukemia (B-ALL).[25] And CD22 expression was only limited to B lymphocytes.[22] Another key advantage is the intrinsic functionality of CD22. CD22, as a part of a co-receptor on the surface of B cells, participates in the negative fine-tuning of BCR(B cell receptor) signaling mediated by continuous crosstalk with different cells[22]. Considering the effect of this molecule on the membrane dynamics of target cells, it is conducive to the accelerated endocytosis of drug molecules by target cells after antibody-specific binding.[22] Therefore, after comprehensively considering, CD22 is an excellent target molecule of the tumor cell.

4.4 Lymphomas

Lymphomas is a cancer of the lymphatic system, which have two main types of lymphoma: Hodgkin's lymphoma and non-Hodgkin's lymphoma. There are differences between Hodgkin's lymphoma and non-Hodgkin's lymphoma. Hodgkin's Lymphoma is a cancer starts in white blood cells [26]. Non-Hodgkin's lymphoma, also called NHL or just lymphoma, is a cancer that starts in cells called lymphocytes, which is an important part of the human immune system [27]. For both lymphoma, monoclonal antibodies were widely used to treat by targeting different antigens. Lymphomas related diseases can cause symptoms of painless swelling of lymph nodes, itchy skin, fever, unexplained weight loss, shortness of breath, night sweats, persistent fatigue, etc [28]. Though the reason causes lymphoma is still unsure, the lymphoma started by a genetic mutation on a white blood cell called a lymphocyte [26]. This mutation has the ability to keep cells alive when other common cells died. This causes the lymph nodes, spleen, and liver to swell due to deposition of dead, ineffective diseased lymphocytes in the lymph nodes.[28]

4.4.1 Treatment in Hodgkin's Lymphoma

Anti-CD30 anitibodies are widely used in the treatment of Hodgkin's Lymphoma because Hodgkin Lymphoma is characterized by malignant Reed-Sternberg cells which express CD30 [29]. As a marker of large cell lymphoma, CD30 is an activation antigen and is widely expressed in an uncertain number of immunoblots in reactive lymph nodes. The expression of CD30 is characteristic of large lymphocytes in primary cutaneous CD30 positive lymphoproliferative disorder [30]. To target CD30 and treat the lymphoma, Brentuximab vedotin, known as Advetris, is used. It is an antibody-drug conjugate that it is a collaboration of a chimeric anti-CD30 antibody, IgG1, linked with the drug monomethyl auristatin E with a linkage [31]. (The IgG1 antibody makes the Bretuximab vedotin to target tumor cells that are expressing CD30. After the Brentuximab vedotin enters the cell, the linker is broken and releasing MMAE with binds disrupts the microtubule network label. MMAE is a microtubule-disrupting particle that it covalently attaches to the antibody by a linker [31]. The binding of MMAE to tubulin will disrupts the microtubule network within the cells, which will induce the apoptosis of the malignant cells.

In clinical trial, SGN-30, known as cAC10, is a monoclonal antibody targeting CD30 antigen [32]. It is constructed from the variable regions of the anti-CD30 murine monoclonal AC10 and the human gamma 1 heavy chain and kappa light chain constant regions[16]. Its safety and tolerability have been approved and evaluated in phase 1 multidoes study that the treatments were well tolerated and didn't reach the maximum tolerated dose.[32],[33] Though some four grade III/IV adverse events were reported at a relatively high dose, the relationship between these adverse events and SGN-30 is unknown, and the mild adverse events have no relationship to doses [32].

On the hand, brentuximab Vedotin (SGN-35) is a conjugates anti-CD30 antibody, which have a better treatment effect than unconjugated antibody such as SGN-30 [15]. SGN-35 can stop cell cycle and lead to apoptosis by releasing MMAE to the cell because it attaches the antitubulin agent monomethyl auristatin E (MMAE) to itself via an enzyme-cleavable dipeptide linker [32]. The drug is well tolerated in all dose levesl and has minor adverse events generally in grade 1 or 2 [32].

4.4.2 Treatment in Non-Hodgkin's Lymphoma

CD79 is a signal component for the B-cell receptor for Non-Hodgkin's Lymphoma's treatment which expresses only on B cells and in most non-Hodgkin's Lymphomas. CD79b(Ig-beta) is one of the covalent heterodimer molecule that contains an extracellular Ig domain, an intracellular signaling domain, and a transmembrane domain[13]. The B-cell receptor is a complex between CD79 itself and surface Ig. BCR (B-cell receptor) can lead to apoptosis by triggering its signaling by its cross-linking function [13]. In addition, due to the CD79's feature of targeting MIIC (a lysosome-like compartment), drugs can only be released in the targeted cells with more stable linkers [13].

Anti-CD79b-MCC-DM1 and anti-CD79-MC-MMAF are the antibodies that target-dependent killing of NHL cells in vitro. Also, they are as effective as in low doses in xenograft models of mantle cell, follicular, and Burkitt lymphomas [13]. As shown in the figure below, regardless with the cell line usage, both anti-CD79b-MCC-DM1 and anti-CD79-MC-MMAF perform similar efficacies even though the drug chemistries and linkers are different [13].

4.4.3 Treatment for both Hodgkin's Lymphoma and Non-Hodgkin's Lymphoma

CD20, a B cell marker, is a molecule embedded in the membrane surface that plays a role in the development and differentiation of B-cells into plasma cells. Even though knocking off CD20 from the mice does not apply any obvious phenotype changes, CD20 is still important in the treatment for both Hodgkin's Lymphoma and Non Hodgkin's Lymphoma [34]. CD20 is identified as a modulator of cell growth and differentiation and is involved in B-cell activation, differentiation, and growth [35].

Rituximab, also called Rituxan, is widely used to treat nodular lymphocyte-predominant Hodgkin lymphoma (NHPHL) by targeting CD20 antigen.[36] It is the first therapeutic anti-CD20 mAb and it is a murine-human chimera antibody that multiple patients have response to it [33]. Rituximab is often given at the same time with radiation therapy and/or chemotherapy [36]. As a chimeric antibody, Rituximab contains human IgG1 immunoglobulin, whose isotype is efficient in activating Fc receptors and C1q [35]. Binding of Fc receptor can create antibody-dependent cell-mediated cytotoxicity because it is responsible for natural killer cells that recognize IgG1 or IgG3 opsonized tumor cells [35]. Furthermore, the involvement of Fc receptor may induce the expression of Fas ligand, which may induce apoptosis in Fas-expressing tumor cells [35]. In addition, the connection between Rituximab and the CD20 may lead to the anti-proliferation effect [35].

To increase the effectiveness, tolerance and to lower the immunogenicity, more humanized anti-CD20 monoclonal antibodies are developed [33]. The second generation of the anti-CD20 mAbs includes humanized mAbs: ocrelizumab, and veltuzumab, and the fully human mAbs: ofatumumab [33]. The second generation anti-CD20 mAbs has been approved for being used in treatment. Ocrelizumab is a type I second generation humanized mAbs with multiple differences in amino acid positions within the CDRs [37]. It have the ability to enhance the efficacy and increase binding affinity to the FcγRIIIa receptor[37]. For Veltuzumab, it has stronger CDC effect and binding affinity compared to Rituximab. Due to the structural difference, it lowers the CDC cell toxicity.

There are also third generation anti-CD20 mabs, which have engineered Fc region. This can help to increase their binding affinity with the FcγRIIIa receptor. Ocaratuzumab, a type I humanized IgG1 mAb, have the mechanisms to overcome the lower response rates and shorter duration of the responses to rituximab due to the increase binding affinity to FcγRIIIa receptor [37].

4.4.4 PD-1

PD-1 is a protein on T cells that keep the T cells from attacking other cells. Nivolumab and pembrolizumab are the medicine that block the PD-1. Nivolumab is a human immunoglobulin G4 (IgG4) that binds to the PD-1 and blocks its interaction with PD-L1 and PD-L2 by disabling proliferation and cytokine production in the T-cells [35]. Pembrolizumab, a therapeutic antibody, that binds to and blocks PD-1. PD-1 receptor on activated T-cells binds to the PD-L1 or PD-L2 and deactivate any potential cell-mediated immune response against the cells. Thus, the immune system can kill cancer cells by blocking PD-1 since it can lead the T cells to kill cancer cells.

Nivolumab and pembrolizumab are mAbs targeting PD-1 antigen. They have tolerable adverse events and similar effective result in treatment[38]. Compared with Nivolumab, pembrolizumab have less any grade adverse events such as fatigue and rash.[38] About the difference between treatment on Hodgkin's lymphomas and non-Hodgkin's lymphomas, patients with Hodgkin's lymphomas (HL) have a better response than patients with non-Hodgkin's lymphomas (NHL) that HL has a rate of 69.08% while NHL has a 30.77% responses [38].

CD19, a 95-kDa transmembrane glycoprotein in the immunoglobulin super family, can act 12

as a central positive response regulator in B cells [39]. The expression of B- lineage cells and follicular dendritic cells of CD19 plays a significant role in B cell diseases. Though CD-19 is a less effective marker for B-cell lineage compared to CD-20 because it starts expressing at the pre-B cell stage, several CD19-targeted monoclonal antibodies were developed and tested to treat CD-19 positive lymphomas and autoimmune diseases

In clinical trials, multiple new CD-19 targeted monoclonal antibodies for the NHL treatment are under process. There are more than 30 antibody drug conjugates are under investigation of clinical trials. IgG1 antibodies with cytotoxicity improved Fcγ part such as SAR3419 and denintuzumab are in phase 1/2 trials. The most advanced anti-CD19 antibody, blinatumomab, for the NHL treatment is in phase 1, and it has been approved for Precursor B-cell acute lymphoblastic leukemia in Dec 3, 2014.

5. Conclusion

Over the past decade, development of the cancer drugs has been approved dramatically, and mAbs have been emerged as one of the most popular topics in the treatment of cancer instead of Chemotherapy or surgery. In clinical trial, however, we still have a long way to go in the development of the available medicine. In this article, we reviewed different mAb drugs most generated by the humanized or human mAbs, such as ipilimumab, trastuzumab or ramucirumab, which have less rejection reaction in human body. We concluded the potential possibility of different mAbs related drug used in the treatment of the lung cancer, breast cancer, lymphomas and leukemia. Over almost all of the mAbs drugs, they have a significance in the treatment of different cancer. On the other hand, some clinical applications of some drugs are still unclear or don't have enough experiment support. In the future, more laboratory experiment and clinic trial would rich the mAbs drugs with more efficiency in diminishing the symptoms of cancer and less side effect.

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