Gemtuzumab Ozogamicin: A Drug Used to Treat Acute Myeloid Leukemia

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Abstract: Acute Myeloid Leukemia (AML) is one type of Leukemia, which is the most common type of Acute Leukemia (AL), almost 90% of types of AL are AML. Gemtuzumab Ozogamicin (GO), which is also called MYLOTARG, is a kind of drug used to treat AML. It is targeted at CD33, which is a typical receptor on AML cells, and it will not express in normal hematopoietic stem cells and mature granulocytes. Cell experiments illuminated that GO could specifically kill cells that expressed CD33 and secure for other cells. After GO returned to the market in 2017, more and more doctors try to use it in the clinic. Based on the clinical data, GO shows higher safety and effectiveness in young patients than the aged. And patients who express CD33 at a high level could get more benefits from GO. Other factors like specific genotypes or disease courses also need to be a consideration. This paper focuses on the mechanism, development history, clinical application, and the disadvantage and limitations of GO, and the performance of GO is analyzed in the treatment of AML both independently and in combination with chemotherapy or other drugs, like decitabine, cytarabine, daunorubicin, etc.

1. Introduction

Leukemia, which is also called blood cancer, is a kind of hematopoietic stem cell malignant clonal disease. Clonal leukemia cells proliferate and accumulate in the bone marrow and other hematopoietic tissues, infiltrate other non-hematopoietic tissues and organs, and inhibit normal hematopoietic function due to the mechanism of uncontrolled proliferation, differentiation disorder, and blocked apoptosis. Patients who get Leukemia will have different degrees of anemia, bleeding, fever and liver, spleen, lymph node enlargement, and bone pain.

In 2016, World Health Organization (WHO) has classified Leukemia into four types: Chronic Lymphocytic Leukemia (CLL), Chronic Myelogenous Leukemia (CML), Acute Lymphocytic Leukemia (ALL), and Acute Myeloid Leukemia (AML). CLL is most common in adults, CML is common in adults and men, ALL is common in children, teenagers, and adults lower than 39 years old, and AML is the most common type of acute leukemia [1]. A recent study showed that in 2018, the average age of the patients who got AML was older adults above 67 years old, and 54% of the patients were above 65 years old, the risk of getting AML will increase with the rising in age [2]. The reason why people get AML may be exposed to some special kinds of RNA-virus, chemical substance, radiation environment, or have hereditary factors. However, some people have may sudden onset of leukemia, and the exact reason why they get the disease is still not understood exactly.

Gemtuzumab Ozogamicin (GO), which is also called MYLOTARG, is produced by Pfizer Inc. to treat AML. It can be used by CD33+ patients older than 2 years old, which means that it can be used for AML indications in children. And this is an amazing point of this drug.

GO is a kind of monoclonal IgG4 antibody consisting of humanized murine CD33 monoclonal antibody and Deoxyribonucleic acid embedding agent calicheamicin (CLM) [3]. It is first approved by U.S. Food and Drug Administration (FDA) in 2000, however, it was voluntarily withdrawn from trials on October 12th, 2010 because the trials failed to show its improvement in survival and increased treatment-related mortality. On September 1st, 2017, GO was approved by FDA again for the treatment of adults with newly diagnosed CD33+ AML for patients who had experienced a relapse or had not responded to initial treatment. It was the first antibody-drug conjugate approved for human use by the FDA [4].

This paper focuses on the mechanism, development history, clinical application, and the disadvantages and limitations of GO, to learn its performance in treating AML and find out its possible ways of improvement.

2. The History of monoclonal antibody therapy

2.1 the rise of monoclonal antibody therapy

In 1979 Lee Marshall Nadler decided to explore the potential utility of new technology, monoclonal antibodies. In April 1979, N obtained NB tumor specimens and immunized mice with this material. The immune systems of the treated mice responded and produced many different antibodies. They envision that making monoclonal antibodies might help prevent the antibodies from attacking benign human tissue, and perhaps even produce tumor-specific antibodies. They succeeded in finding a monoclonal antibody (Ab89) that effectively attacks cancer cells and can distinguish them from healthy human cells.

They began clinical trials soon after the approval. The patient had no severe allergic reaction, but no antibodies were found on the cancer cells. After increasing the concentration of the drug. Although there are fewer tumor cells in the blood, this is only temporary. In subsequent studies, the patient was injected with more than 1500mg antibody at a time, but the interfering components in its blood still affected the effectiveness of the antibody. Although NB died after treatment due to disease deterioration, this study proved the feasibility of monoclonal therapy. It alerted the N team to the idea of finding antibody targets in the future.

2.2 Drug Development History

After confirming the drug's activity in a xenograft model, a Phase I dose-escalation study was conducted in 40 patients with relapsed/refractory aML. Morphologically detectable ELIMINATION of aML occurred in 20% of patients, and 12.5% achieved complete remission (CR) or incomplete platelet recovery (CRP). The dose increase stops at 9mg/mq because the dose effectively saturates the amlcd33 binding site, even in patients with a large number of circulating mother cells. However, later results suggest that this measurement may far exceed the concentration of effective binding sites for CD33.

In the study leading to the original accelerated approval of GO, the observed toxicities of GO at 9mg/mq included infusion-related toxicities (chills, fever and mild hypotension), the significant myelosuppression expected when targeting an early myeloid differentiation antigen, and mild, transient bilirubin elevations seen in 23.0% of patients.13 Only 1 patient had a bilirubin elevation beyond 10xnormal, and as a result, GO dosing 6-9mg/mq was often chosen for subsequent studies. As the drug began being used in more heavily pretreated patients or combination with other agents, an increased incidence of toxicities – particularly SOS, began observed. 17-19 Subsequent pharmacokinetic (PK) analyses indicated that the originally approved dose of GO may have been too high, leading to excess toxicity.

Data from mathematical models suggest that intracellular exposure to a fixed dose of GO is primarily dependent on the number of CD33 positive myeloblasts in the blood, cd33 antigen production rates, and aBc transporter activity, rather than the cd33 density on the cell surface

The body. Data from laboratory and clinical studies have correlated several variables related to GO uptake and drug transporter activity with outcomes after oxyfossilene treatment and confirmed the predictions of these mathematical models. Customizing go dosing based on go uptake and cac sensitivity, rather than a fixed dose for all patients, may increase the risk/benefit ratio of GO.

3. The Mechanism of GO

3.1 GO binding with CD33 antigen

CD33 is a sialic acid-binding Ig-like lectin, which is a member of the immunoglobulin superfamily subset of sialic acid-binding immunoglobulin-related lectins. It is considered an inhibitory receptor that negatively regulates cell proliferation and activation. It is expressed in 90% of AML cells, but not in normal hematopoietic stem cells and mature granulocytes. Therefore, CD33 is a good target for treating AML [5]. There are two tyrosine residues sequences in the cytoplasmic tail that are very similar to the immune receptor tyrosine suppressive motifs (ITIMs). When these two tyrosine residues sequences are phosphorylated during pharmacological treatment and receptor crosslinking, they can provide docking sites for recruitment and activation of tyrosine phosphatases (SHP-1 and SHP-2) in the Src homolog-2 (SH2) domain. The activation of CD33 and association with SHP-1 may result in inhibition of signal transmission and may affect the function of adjacent membrane receptors [6].

CLM is a family of enediyne antitumor antibiotics that were isolated from the fermentation broth of Micromonospora echinospora, a kind of bacteria. It contains four carbohydrate residues, a hexasubstituted benzene ring, an unusual N-O glycosidic linkage, a trisulfide moiety, and a bicycle [7.3.1] trades-9-ene-2, 6-diyne system. It can cut DNA in location-specific double-stranded ways. After binding to DNA grooves, it can reduce. As a result, the product rearranges to form 1, 4-dehydrobenzene diradicals, which can cause conformational changes in binding domains by extracting hydrogen from DNA and initiating double-strand cleavage [7]. This will cause double-strand breaks and apoptosis [8]. In this way, tumor cells will die.

When the drug is binding with CD33 antigen, cytoplasmic immune-receptor tyrosine-based inhibitory motifs (ITIM) will phosphorylate, probably mediated by LCK, one of the kinases from the Src Family Kinase (SFKs). This will help to stimulate endocytosis of the GO-CD33 compound, and then, GO will rapidly internalize.

When the GO-CD33 compound is translocated into Lysosomes, the bifunctional acid-hydrolyzable linker between the antibody and calicheamicin will cleave in the acidic environment, this will lead to the release of calichDMH derivative. And then, CalichDMH will be reduced by glutathione to form the 1,4-dihydrobenzene-diradical (caliche-γ1).

After that, the molecule compound will bind to the minor groove of DNA, which will cause conformational changes in the binding domain. This will cause double-strand breaks and apoptosis. And this process will affect the normal physiological function of cells. Thus, in this way, tumor cells will die [9] (figure 1).

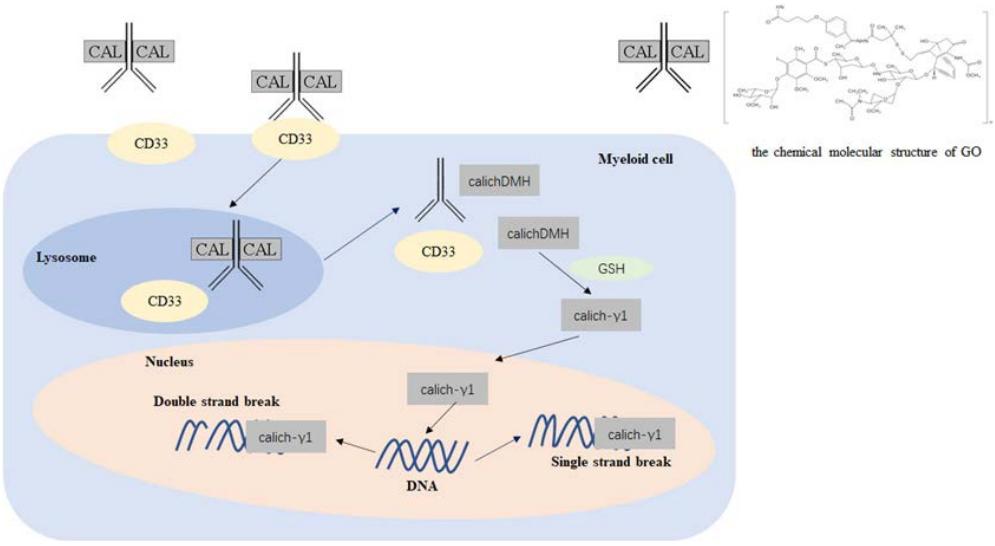

Figure 1. The mechanism of GO in vivo. When the drug is binding with CD33 antigen, it will internalize and calichDMH will be released, and calichDMH will be reduced by glutathione to form the 1,4-dihydrobenzene-diradical species, a kind of potent antitumor antibiotic. After that, the molecular compound will bind to the minor groove of DNA, and this will lead to the death of CD33+ cells [9].

3.2 MDSCs Targeting with GO

Recent research shows that GO can also help to treat AML by targeting at Myeloid-Derived Suppressor Cells (MDSCs). MDSCs are a group of heterogeneous cells derived from bone marrow, and are the precursors of Dendritic Cells (DCs), macrophages and granulocytes. These cells have the ability to significantly inhibit the immune cell response. Under normal circumstances, MDSCs can rapidly differentiate into mature cells, and then, these mature cells will enter the organs and tissues, so that the immune system will work normally.

However, in tumor cells, due to the action of cytokines, the maturation of MDSCs will be blocked, and remain at various stages of differentiation, they will accumulate in the tumors and blood of patients. This will later lead to an immunosuppressive microenvironment in vivo.

L. Fultang, et al. suggest that GO can help to deplete MDSCs in cancer patients, which can overcome the immunosuppressive microenvironments in vivo to reactive the immune proves mediated by T cells. CD14+ (M-MDSCs) and CD15+ (G-MDSCs) are two types of surface target of MDSCs. Compared to G-MDSCs, GO will mostly combine with M-MDSCs, and will rapid immunotoxin internalization. GO will induce the viability of M-MDSCs from the tumor CD33+ cells, and this ability will decrease with the decrease of drug dose, but it will not affect CD33- cells. Suppressive tumor will polarize CD33+ cells, decrease the level of HLA-DR and raise the level of CD68. GO treatment will also lead to the increase level of pATM, which is the same as the DNA-damage caused by CLM, and then, tumor cells will experience losing the integrity of cell membrane, nuclear condensation, and blebbing. This shows the death of the tumor cells.

This finding has potential clinical importance for CAR-T therapies against solid tumors since MDSCs can suppress the proliferation of CAR-T cells and can also damage the cytotoxicity of CAR-T cells. As we mentioned above, GO can help to deplete MDSCs, it can improve the CAR-T construct efficiency, this can lead to a further significant reduction in viable mesothelioma and neuroblastoma cells. Thus, it can provide treatment to improve CAR-T cell activity [10].

4. Clinical application of Gemtuzumab ozogamicin (GO)

The clinical application results of GO in different situations. Include newly diagnosed AML or refractory AML, child patient or senile patient, single-use of GO, or combine with other therapy. Based on the clinical data, the therapy effect and security have an obvious difference in different kind of

patients, especially the elderly. Patients over 60 years old show lower survival rates. Moreover, the use of GO with other therapy could reduce the side effect.

4.1 Single use of GO

As a targeted drug, the pharmacological action of GO is clear. However, its actual clinical performance is not promising. Many patients experienced various adverse reactions after using the drug. Not every patient will be able to extend their life and bone marrow transplant time with GO. However, considering that no other targeted drugs have been approved for the treatment of AML, and conventional chemotherapy is not ideal. GO has become a viable option for patients who are not eligible for conventional chemotherapy.

The single-use of GO data is great statistics to certify the therapy effect, but in the traditional, clinical treatment of diseases is mostly by combination use of drugs to achieve the best therapeutic effect. As a result, clinical data for the use of a single drug is almost impossible to acquire. Only in specific situations, researchers could record the single-use of GO result.

From the report of I Alvarez-Twose [11] and Hiroko Tsunemine [12], single-use of GO showed the curative effect. A 69 years old female who has mast cell leukemia tried many types of treatment but none of them relieve her symptom. With the single-use of GO after 2 months, the sT level normalized which was accompanied by improvement in cytopenias and ultimately, transfusion-independence. Another 68 years old female single used GO in a period of 24 months, her early relapse AML was hematological remission sustained over these 24 months. Even if these two patients were treated through GO, they were not statistically significant. More data are needed to prove the effectiveness of single-use of GO.

4.2 Combination therapy

Drug combinations are more widely used than drugs alone. Both for better efficacy and lower side effects. There are also patients who have to be treated with multiple drug combinations because of resistance or specific adverse reactions. N Daver reported 110 patients got four different kinds of AML [13], used GO with decitabine. After 24 cycles of therapy (4-8 weeks each), the response rate was improved and the death rate was reduced. The statistics from 1022 de novo AML children’s patients [14], using chemotherapy with GO did better than using chemotherapy only. For relapse AML, recorded by Maya Koren-Michowitz[15], 16 adult patients therapy consisted of ARA-C (1 gr/m2) for 4 days followed by one dose of GO 9 mg/m2 on day 5 and was supported by donor stem cells when possible. After 1 year, 25 % of patients were alive; however, all had relapsed again. Etienne Paubelle in 2017 [16] reported 24 very high-risk AML patients. Patients used GO and meanwhile combined with intermediate-dose cytarabine and daunorubicin to save their lives. After 36 months, complete remission was achieved in 50% of cases (46% in refractory and 55% in relapsed AML) without excessive toxicity. The combination can improve the situation for some patients, but patients still need to face the risk of side effects and failure in treatment. It is important to find out which patients are better candidates for GO therapy.

4.3 Influence from patients themselves

Fortunately, researchers are already using statistical methods to determine which patients suit for GO therapy. Based on age and gene expression is the reasonable way of classification currently.

In the research from N Khan [17], 1583 AML patients have divided into two groups--old and young to obvious the result of use GO under the dose of 3mg/m2 or 6mg/m2. This is a long period of research, as the result says the efficacy was correlated with human leukocyte antigen expression level and patients' age. The expression level of CD33、CD34 and CD38, these directly related to efficacy and recurrence rate. Because GO needs to identify CD33 and kill cancer cells. And in this research, the old group were more difficult to get benefits from GO therapy. Roya Rafiee's report in children’s patients [14], also found evidence that the curative effect relative to ABCB1 SNP genotype.

These studies lay the foundation for the rational use of GO. But there's still no guarantee that every patient will get the suitable treatment. For AML, which is difficult to cure, even a limited cure rate like this is a breakthrough. The table 1 summarizes the date of several applied literatures.

Table.1. Clinical research in use of Gemtuzumab ozogamicin.

Type of disease	Sample	Therapy	Time of therapy	Therapeutic effect	Ref.
Mast cell leukemia	A 69 years old female	Single use of GO	2 months	The sT level normalized which was accompanied by improvement in cytopenias and ultimately, transfusion-independence.	[11]
AML in early relapse	A 68 years old female	Single use of GO	24 months	Hematological remission sustained over 24 months	[12]
Four kinds of AML	110 patients	Use GO with decitabine	24 cycles of therapy (4-8 weeks each)	Response rate was improved and death rate reduced. Did better in youth.	[13]
De novo AML	1022 children	Chemotherapy with GO	Over 5 years	Use with GO did better than chemotherapy only. And the curative effect relative to ABCB1 SNP genotype.	[14]
Relapse AML	16 adult patients	Therapy consisted of ARA-C (1 gr/m2) for 4 days followed by one dose of GO 9 mg/m2 on day 5 and was supported by donor stem cells when possible.	1 year	After 1 year, 25 % of patients were alive; however, all had relapse.	[15]
Very high-risk AML	24 very high-risk AML patients	GO combined with intermediate-dose cytarabine and daunorubicin.	36 months	Complete re-mission was achieved in 50% of cases (46% in refractory and 55% in relapsed AML) without excessive toxicity.	[16]
Normal AML	1583 patients were grouped according to age	GO was given at 3mg/m2 or 6mg/m2.	Long period research	The efficacy was correlated with CD33 expression level and patients' age.	[17]

Gemtuzumab ozogamicin is the first approved drug for the treatment of AML with CD33 targeting and has shown some efficacy in CD33 positive patients, including adults and children. In 2010, although, GO exited the market because of its security and effects, the clinic trial of GO didn't stop. Since 2017, GO has been appearing on the market again. A cautious attitude is needed in treating GO. As to whether a patient should choose to receive GO treatment, many factors such as age, genetics, and disease course should be considered. In addition, to know whether the AML patients have any myelodysplasia-related changes or are therapy-related is also important [18].

It should be pointed out that the optimal dosage and therapy of GO still need to be confirmed. Therapy in different drug combinations also needs further research. Large-scale clinical use of GO remains many limits. This has to do with the side effects and unclear efficacy of GO.

5. Adverse reactions of GO

Many adverse reactions have been reported in patients treated with GO, including thrombocytopenia and hepatic injury. There were almost 13% of patients who experienced persistent thrombocytopenia in phase II clinical trials [19]. This was also one of the main reasons for unwanted dose reduction and withdrawal of treatment. Sinusoidal obstruction syndrome (SOS) is a potentially fatal hepatic disease, and its clinical manifestations include jaundice, hepatomegaly, weight gain, and ascites [20].

5.1 Thrombocytopenia

There was an experiment to investigate the mechanism of thrombocytopenia caused by GO. PF-0295 was a nonbinding antibody–calicheamicin conjugate and contained same linker-payload as GO. Researchers injected PF-0295 into cynomolgus monkeys and necropsied them. The result showed that PF-0259 induced an obvious decrease in platelet concentration in monkeys, which was caused by SEC injury and platelet sequestration [21]. In a phase 3 trial, haematological toxicity was more common in the GO group. 16% of patients in GO group and 3% in control group were observed persistent grade 3 and 4 thrombocytopenia [22].

5.2 Sinusoidal obstruction syndrome (SOS)

An analysis of clinical trials by the academic initiative indicated that 99 patients experienced SOS among the 221 GO-treated stem cell transplants (SCT) and 649 who did not undergo SCT. 15% SOS presence when GO was administered as monotherapy and increased to 15% - 40% if SCT was undergone with 3 months of first GO administration. The death occurred in 33% of patients caused by SOS in this case. 80% of SOS patients experienced some symptoms including elevations of hepatic aminotransferases, painful hepatomegaly, ascites, or weight gain [23]. In another study, 36(15%) patients developed SOS within 248 patients who had been treated with GO [24].

In conclusion, gemtuzumab ozogamycin (GO) made a great contribution to the treatment of acute myeloid leukemia (AML), but it can also induce some dangerous adverse reactions, including thrombocytopenia and sinusoidal obstruction syndrome (SOS). As a result, the administration of GO requires special caution, and more research is needed for future development.

6. Conclusions

Recently, there is still an urgent need for an improved treatment for AML. GO is currently one of the mainstream drugs used in the treatment of AML. It can kill the abnormal cells by targeting CD33, which is a typical receptor on AML cells, and binding with the minor groove of DNA. However, the therapeutic effect of the drug is unsatisfactory. By studying the clinical application results of GO in different situations, we find out that GO is seldom used alone to treat AML because of its various side effects and low efficacy. When GO is used in combination therapy, the situation is better. Its toxicity drops and efficacy rises. But its side effect is still a serious problem since patients who used this drug may come up with some dangerous adverse reactions like thrombocytopenia and SOS. So further

experiments are needed to reduce its toxicity by reducing the dosage, increasing its efficacy by combing it with different drugs, and making sure how to make a specific treatment plan for patients of different ages, genetics, and disease course. We are sure that the efficacy of GO will be further improved, and new drugs used to treat AML will come out in the near future. We will finally find out an ideal treatment for AML.

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