Current status of immunotherapy in acute myeloid leukemia

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Abstract. Acute myeloid leukemia (AML) is a rapidly progressive, poor prognosis malignant tumor caused by hematopoietic stem cells/progenitor cells. In recent years, there have been significant advances in basic and preclinical research on AML. Compared with traditional chemotherapy, hematopoietic stem cell transplantation (HSCT) significantly improved prognosis. However, with high recurrence rates and low 5-year survival rates, more and more attention has been focused on immunotherapy strategies for AML. Given the immunological characteristics of AML and the mechanisms of immune escape, ongoing efforts are aimed at improving the strategy of immunotherapy and the design of novel therapies, such as vaccines, monoclonal antibodies, chimeric receptor-engineered T cells (CAR-T), and checkpoint inhibitors, which hopefully can deliver higher specificity and efficacy in AML therapy. In this review, we provide an overview of the immunological characteristics of conventional AML therapies, explore immune avoidance mechanisms, and describe the mechanisms of active and passive immunotherapies and current clinical trials.

1 Introduction

Acute myeloid leukemia (AML) is a fast-growing malignant blood cancer caused by the overproliferation of progenitor cells at different stages of myeloid primitive cell development. In AML, primitive myeloid cells and immature myeloid cells in bone marrow and peripheral blood go through abnormal proliferation, leads to rapid growth of a large number of abnormal cells in bone marrow and blood, which interferes with normal hematopoietic function of the human body. They prevent the marrow from making normal red blood cells, white blood cells and platelets. With fewer healthy blood cells, the body can’t fight infections or stop bleeding. The clinical manifestations include anemia, dyspnea, abnormal metabolism, blood stasis, hemorrhage, infection, fever, etc. The exact cause of acute myeloid leukemia remains unclear, but is associated with the environment, ionizing radiation, chemical exposure, use of alcohol and tobacco, and specific responses to certain viral infections. In addition, recent studies on the frequency of gene mutations and some susceptible biomarkers have found that AML may be the result of genetic and environmental factors.

2 Traditional treatments for AML

2.1 Hematopoietic stem cell transplantation (HSCT) for AML

Bone marrow or blood hematopoietic stem cell transplantation (HSCT) is a traditional treatment for patients who have AML. It replaces the unhealthy blood-forming cells (stem cells) with healthy ones. After achieving a first complete chemotherapy-induced remission (CR1) in AML, a postremission therapy is necessary to prevent disease relapse. Myeloablative conditioning followed by allogeneic stem cell transplantation (alloSCT) is the earliest immunotherapy modality that is still widely used and is an effective treatment option for young AML patients in CR1.[1] Donor’s healthy natural killer cells and T lymphocytes recognize and target the malignant cells and replace them. For some people, transplant can cure their disease.

2.2 Immune system against AML

GVL is a graft-versus-leukemia effect closely associated with allogeneic hematopoietic progenitor cells and stem cell transplantation. The GVL effect is the underlying reason why stem cell allografts can cure hematologic malignancies [2]. The natural killer cells and T lymphocytes can recognize and target the recipient’s malignant cells. It was found that the rate of leukemia recurrence in patients with acute or chronic graft-versus-host disease (GVHD) was 2.5 times higher than in patients without GVHD. In addition, the recurrence rate of leukemia was higher in patients with the syngeneic bone marrow transplantation than in patients with the allogeneic bone marrow transplantation. Therefore, it is speculated that the donor lymphocytes may have a certain degree of attacking effect on the leukemia cells in the recipient, which is called the GVL effect.

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2.3 Immune escape in AML

Studies show that both the innate and adaptive immune systems can recognize AML cells, eliminate leukemia cells or maintain a balance to prevent tumor growth.[3] AML cells are impressionable to T cells and NK cells attack by expressing co-stimulating molecules and ligands of leukemia-associated antigens, MHC and NK cell-activated receptors.[4] Natural killer (NK) cells, the backbone of the innate immune system, support the development of an effective adaptive anti-tumor immune response by secreting cytotoxic and cytokines that exert direct anti-tumor effects and indirectly contribute to tumor control through communication with other immune cells.[5]

Natural killer cells, T cells, and dendritic cells (DC) play an important role in the immune monitoring of acute myeloid leukemia, so their anti-leukemia properties have been applied to different immunotherapy strategies. Although NK cells can target cancer cells and have been shown to be useful in AML immunotherapy, some hematologic malignancies, including AML, can cause NK cell function to significantly impaired. Thus, AML can escape the immune surveillance of NK cells through a series of mechanisms that contribute to the dysfunction of the immune response, leading to immune escape.[5]

In this context, clinical trials have explored multiple vaccines, cytokines, and therapies to enhance T-cell immunity, improve target cell sensitivity, and strategies to directly attack AML cells to overcome immune escape.[6] Despite advances in AML treatment in recent decades, survival rates have not improved significantly due to the limitations of treatment and high incidence of leukemia recurrence, suggesting the need for new treatments.[7, 8]

In addition to the emerging field of chemotherapy and targeted therapies, immunotherapy for AML is an important and attractive area of research.

3 Immunotherapy for AML

3.1 Active immunotherapy

Active tumor immunotherapy is to inject the tumor antigen and let it induces the innate immune effector cells, which identify the specific tumor antigens, mediate specific immune response and secrete antibodies. The most commonly used are vaccines. Tumor vaccines Researchers have been worked on the tumor vaccines for long and some types of vaccines are used in AML treatment. Most clinical trials have shown effects and clinical benefit in AML, such as peptide vaccines[9, 10], DNA vaccines[11] and dendritic cell-based vaccines[12, 13].

3.1.1 Autologous whole AML cell vaccines

Tumor cell vaccines use modified autologous whole tumor cells to stimulate the organism to produce an anti-tumor response. Considering the AML cells surface contains lots of known and unknown antigens, autologous whole AML cells seem to help stimulate AML specific immune responses against multiple antigens, providing therapeutic vaccines for specific individuals. This kind of vaccines can effectively reduce the probability of immune escape. Studies have been done on trials using autologous whole AML cells, revealing the immune response was increased as the result of autoimmunization. [14]

![Fig. 1. Immunotherapy for AML. Created with BioRender.com](https://example.com/fig1.png)
3.1.2 Peptide vaccines

Peptide vaccines are vaccines that induce immune responses prepared by chemical peptide synthesis techniques based on the amino acid sequences of certain epitopes known or predicted from leukemia-associated antigens (LAAs).[15] Peptide vaccines are often synthetic vaccines and resemble naturally occurring proteins from pathogens. Peptides from tumor-associated antigens are used to induce effective anti-tumor T-cell response.

Peptide vaccines developed for AML have been used in clinical trials against different leukemia-associated antigens, such as protease-3-derived epitope peptide (PR1), Wilms tumor 1 (WT1) antigen, hyaluronic acid-mediated motor receptor (RHAMM), and melanoma preferentially expressed antigen (PRAME).[16]

3.1.3 Dendritic cell-based vaccines

Dendritic cells (DCs) are cells that play a role in antigen presentation in the mammalian immune system. Peripheral dendritic cells capture and process antigens, present antigens in the mammalian immune system.

Dendritic cell-based vaccine is a hopeful strategy for the elimination of disease in patients with acute myeloid leukemia (AML), especially for those with high relapse risk and not suitable for hematopoietic stem cell transplantation. Once injected the DC vaccines, DCs can be produced in 3 days and combined with Toll-like receptor signaling-induced cell maturation. These mature DCs bind to RNA encoding the leukemia-associated antigen Wilms tumor protein 1 and secrete the antigen in melanoma to stimulate an immune response based on AML-specific T cells.[12, 13]. Studies have shown that these improved DCs have strengthened capacity for the induction of tumor-specific immune responses in vitro and in vivo.[18-20]

3.2 Passive immunotherapy for AML

Passive immunity is a method by which the body acquires specific immunity by passively receiving antibodies or sensitized lymphocytes. The passive immunotherapy approach is to give patients donated or laboratory-made components of their immune system to help them combat the disease. Passive immunotherapy using antibodies is frequently used in cancer treatment.[21]. Its effects are rapid and has no latency compare to active immunotherapy. Once the antibodies or sensitized lymphocytes enter the body, the patient acquires immunity immediately. To date, several passive immunotherapy strategies have been studied, including adoptive immunotherapy, chimeric antibody receptor engineered T cells (CAR-T), and checkpoint inhibitors. In addition, according to newly study, antibodies to SARS-CoV-2 have potential for therapeutic passive immunization.[22]

3.2.1 Monoclonal antibody therapy

Kohler and Milstein carried out fusion experiments between two known mouse myeloma lines in 1975 and developed a technique for producing antigen-specific MoAbs, that laid the foundation for the possibility of MoAbs to treat tumors.[23] Due to the accessibility to malignant cells in blood and bone marrow, monoclonal antibodies have raised high expectations among scientists for an effective and tolerant treatment of acute myeloid leukemia. Ideal targets represent surface antigens expressed primarily on leukemic blasts while sparing hematopoietic stem cells. In AML, putative targets for antibody targeted therapy include antigens such as CD33 and CD123.[24]

3.2.1.1 Anti-CD33 Antibodies

CD33 is a 67kD member of the sialic-acid-binding immunoglobulin-like lectins (Siglecs), a discrete subset of the immunoglobulin(Ig) superfamily molecules.[25, 26] As a myeloid differentiation antigen, CD33 primarily expressed at very early stages on myeloid progenitors, also on AML blasts in most patients and some leukemic stem cells.[27, 28] CD33 has been the most commonly exploited target in AML treatment due to its expression on at least one subset of leukemic blasts in almost all the patients.

There are plenty of anti-CD33 antibodies that are under clinical trial and proved effective for therapy of AML, like gemtuzumab ozogamicin (GO), SGN33A (Vadastuximab Talirine)[29], IMGN779 (ImmunoGen) [30], etc. GO will be mainly discussed in this review.

An anti-CD33 antibody, gemtuzumab ozogamicin (GO), have been extensively studied for AML therapy, is the best-known MoAb in AML therapy, also a mixture of success and disappointment.[31] GO is a humandized anti-CD33 MoAb conjugated antibody, carrying a toxic calicheamicin-γ1 derivative that, after intracellular hydrolytic release, induces DNA strand breaks, apoptosis, and cell death. GO targets CD33 and rapidly release the toxic part under the acidic condition in the tumor cell lysosomes (pH about 4.0) through hydrolyzable linker.[32, 33]

GO was the first anti-cancer immunoconjugate to obtain regulatory approval from the FDA for older patients with AML in first relapse on the bases of a 30% overall response rate.[34, 35] However, a decade later, a randomized phase 3 clinical trial was conducted to evaluate the potential benefit of adding GO to standard treatment for induction and post-consolidation in patients with AML, and the addition of GO in the study failed to show any improvement in disease-free survival, CR rates, or overall survival.[36] In 2016, another clinical trial was conducted to compare single-agent GO with best
supportive care (BSC) including hydroxyurea as first-line therapy in older patients with acute myeloid leukemia unsuitable for intensive chemotherapy. The results showed that first-line monotherapy with low-dose GO significantly improved the overall survival of these patients compared to BSC, and GO showed undeniable efficacy.[37]

3.2.1.2 Anti-CD123 Antibodies

CD123 is another most common clinically exploited target for MoAb for patients with AML, which promotes increased cell proliferation and survival after combined to interleukin-3 (IL-3Rα)[38], as well as relapse and resistance to chemotherapy in leukemia [39].

The widely known anti-CD123 antibodies include JNJ-56022473 (Talactotuzumab, Variant of Former CSL-362)[40], SL-401 (DT388IL3), Anti-KIR (an antibody against killer-cell immunoglobulin receptor (KIR) on NK cells, lirilumab)[41], etc.

One of the most promising anti-CD123 antibodies nowadays is SL-401 (DT388IL3), a recombinant fusion protein composed of the truncated diphtheria toxin and a human IL-3 ligand[42]. SL-401 is internalized after binding to CD123, resulting in inactivation of protein synthesis and cell death. In addition, the drug has received a breakthrough drug designation from the EU and FDA in October 2017 for the treatment of patients with cystic plasmacytoid dendritic cell tumor (BPDCN).[31] A pivotal Phase 2 trial of SL-401 in BPDCN was presented and showed that across all patients and doses, there was an 84% overall response rate (ORR), and 59% rate of complete response (CR) indicate great potential of SL-401.[43]

3.2.2 Chimeric antibody receptor-engineered T cells (CAR-T)

Chimeric antigen receptor T cells (also known as CAR T cells) are T cells that have been genetically modified to generate artificial T cell receptors for immunotherapy. Engineered CARs incorporate the specificity of antibody recognition of antigens with the co-stimulatory and activation domains of the T cell receptor complex.[44]

Researchers use genetic engineering to activate T cells, and add the tumor chimeric antigen receptors (CAR), to make a CAR-T cells. CAR-T cells use "positioning navigation device" CAR, recognize tumor cells specifically, then release a large number of effectors to effectively kill tumor cells, so as to treat malignant tumors.[45]

The use of targeted CAR T cells in patients with some malignant tumors has been shown to lead to sustained disease remission and extended survival.[46-48] A Study of two children with relapsed and refractory ALL have shown that CAR T cells have the ability to kill even aggressive, treatment-resistant acute leukemia cells in vivo.[49]

3.2.3 Checkpoint inhibitors

Immune checkpoints are molecules that are expressed on immune cells and can regulate immune activation. They play an important role in preventing the occurrence of autoimmunity such as immune function abnormalities that attack normal cells. The expression of immune checkpoint molecules on immune cells inhibits the function of immune cells, which prevents the body from generating an efficient anti-tumor immune response and immune escape of tumors happens.

Important tumor-related immune checkpoint molecules include: PD1, CTLA4, TIM3, and LAG3, of which PD-1 and CTLA-4 are the most widely studied.[50] Immune checkpoint inhibitors are monoclonal antibodies that are developed to target the particular immune checkpoint. Their main role is to block the interaction between tumor cells that expressing immune checkpoints and immune cells, thus blocking the inhibitory effect of tumor cells on immune cells. Additionally, studies have reported that the high expression of PD-L1, PD-L2, PD-1 and CTLA-4 in AML patients. Thus, blocking immune checkpoints is a potential treatment for AML. CTLA-4 and PD-1 will be mainly discussed in this review.

3.2.3.1 CTLA-4

CTLA-4 is a major T-cell co-stimulatory receptor. After the activation of T cells, CTLA-4 expression was induced to inhibit the T cell response.[51] This can prevent autoimmune diseases, but it can also inhibit the immune system from killing cancer cells. Therefore, blocking CTLA-4 can improve the efficacy of tumor immunotherapy. Study indicates that T cells treated with a CTLA-4 blocker showed greater cytotoxicity to autologous AML cells than those treated without CTLA-4 blocker, suggesting that CTLA-4 blockade enhances AML-specific T cell function.[52] Findings revealed that using CTLA-4 blockade after hematopoietic stem cell transplantation (HSCT) can establish anti-leukemic effects if autoimmunity can be controlled.[53]

3.2.3.2 PD-1

PD-1 (programmed death receptor 1) is also an important immunosuppressive molecule. It modulates the immune system and promotes tolerance by downregulating the response of immune system to human cells and by inhibiting the inflammatory activity of T cells. [54] Like CTLA-4, PD-1 is a powerful target for immunotherapy, and has effective clinical applications for cancer treatment. There are many ongoing clinical trials that block the immune checkpoint pathway PD1/PD-L1 and allow patients' T cells to fight leukemia cells being evaluated in patients with AML currently. The large number of ongoing clinical trials of AML immunotherapy will improve
our understanding and enable us to determine the best approach to AML immunotherapy.\textsuperscript{[55]}

4 **Discussion**

In the past few decades, few important breakthroughs in the underlying treatment options for AML have occurred. The introduction of immunotherapy has largely changed the landscape of leukemia treatment, offering hope of survival to more leukemia patients. More immunotherapies are being researched and developed, and the field of immunotherapy for cancer will develop more rapidly and diversify in the future. Immunotherapy will likely be the leading treatment option in the future. Many studies have now confirmed breakthroughs in the efficacy of immunotherapy, and we expect that future immunotherapies will be safer and more effective, combining effectively with conventional treatments for the benefit of more cancer patients.

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