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Immunological therapies targeting leukemia

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Abstract

Leukemia represents one of the greatest challenges in medical oncology due to its aggressiveness and biological complexity. Immunotherapy has recently emerged as a promising option for the treatment of leukemias, however, its genetic complexity has represented a challenge for it. ALL and AML present different genetic alterations, such as mutations, chromosomal rearrangements and signaling pathways. Currently, several therapies have been investigated and applied to try to treat leukemia, among them, CAR T-cell therapy has shown great effectiveness, monoclonal antibodies are another promising option, several immune checkpoint inhibitors have also been developed, the use of CAR-NK cells offers another promising alternative, and as usual, stem cell transplantation remains an important curative option. Leukemia treatments continue to be renewed and updated to make them less toxic and less aggressive for patients.

Keywords: Tumor microenvironment; CAR-T cells; Monoclonal antibodies; Biomarkers; Hematopoietic stem cells; Toxicity in immunotherapy.

1. Introduction

Leukemias, including acute myeloid leukemia (AML) and T-cell acute lymphocytic leukemia (T-ALL), represent one of the greatest challenges in hematologic oncology due to their aggressiveness and biological complexity [1, 2, 3]. Knowledge of these parameters has led to the identification of therapeutic targets for this specific variant, as it can for others [4].

Over the last decade, immunotherapy has been studied as a promising and innovative option in the treatment of many diseases, including leukemias, recalling approaches such as adoptive immunotherapy in AML, described in the 1960s with allogeneic hematopoietic stem cell transplantation (HSCT) [1 ,4, 5]. This advance, based on the graft-versus-leukemia effect, has inspired new therapies including redirected T cells, bispecific activators (BiTE) and checkpoint inhibitors [4]. This article focuses on the analysis of the evolution of these immunotherapeutic strategies and their relevance in the treatment of mainly AML and ALL, with the aim of clearly integrating information from previous research from various popular articles regarding characteristics, cellular markers and current therapeutic approaches in these diseases.

2. Characterization of the main types of leukemias

ALL is a rare hematologic malignancy involving an uncontrolled proliferation of immature lymphocytes in the bone marrow (BM) and blood, with infiltration of other tissues. Advances in chemotherapy have improved the cure rate in pediatric patients; however, treatment options for older adults and relapsed cases remain limited [6, 7, 8, 9]. Common

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symptoms include fever, anemia, bleeding, and bone pain; in severe cases, dyspnea, hepatomegaly, and testicular involvement may be present. Its differential diagnosis is made by cytochemical staining and immunophenotyping of leukemic cells [7].

AML is distinguished by the uncontrolled proliferation of hematopoietic stem cells (HSPC) in the BM and blood, it is more frequent in adults over 70 years of age and has a poor prognosis, presenting differences in the development of the disease and in tolerance to treatment compared to pediatric patients [10, 11], which requires a specific therapeutic approach and stratification with better possibilities [12, 13]. In this the cancer cells interact with the BM microenvironment, creating favorable conditions for their growth. These interactions are mediated by cytokines and chemokines, such as CXCL12, which facilitates adhesion and migration of leukemic cells, reminiscent of the mechanisms of metastasis in solid tumors [10, 14]. The complexity in creating a selective treatment, particularly therapies with chimerical antigen receptor of T cells (CAR-T) for example represents a challenge for immunotherapy, due to the lack of specific antigens on cancer cells that do not affect healthy HSPCs [4, 15].

Chronic lymphocytic leukemia (CLL) consists of an accumulation of abnormal B cells and significant immune dysregulation, is more common in older adults, and although new therapies such as Bruton's tyrosine kinase (BTK) inhibitors and monoclonal antibodies are available, CLL remains incurable in most cases [15].

2.1. Genetics involved in the origin and development of the various leukemias

In the process of leukemic transformation, epigenetic dysregulation refers to mutations in genes encoding epigenome modifiers, which are linked to therapeutic failures [7]. Since 2001, the World Health Organization (WHO) has categorized recurrent genetic groups in myeloid neoplasms, based on particular mutations that affect prognosis and personalized therapy [12]. Modifications in lymphoid development regulatory genes (IKZF1 and ETV6), chromosomal rearrangements (t(9;22) in ALL and AML1-ETO in AML) and signaling pathways, such as tyrosine kinase (JAK1 and JAK2) in ALL, favor cell proliferation [13, 16].

In ALL, recurrent chromosomal translocations, such as TEL-AML1, E2A-PBX1, and BCR-ABL, are common in pediatric B-cell lineage leukemia, with ETV6-RUNX1 reported in 25% of cases [7]. Germline polymorphisms and mutations of drug metabolizing genes, such as thiopurine methyltransferase and glutathione S-transferase, have the ability to modify the response to chemotherapy, in addition epigenetic changes through non-coding RNAs have been mentioned, in addition, epigenetic changes through non-coding RNAs, such as deregulated miRNAs (such as miR-99 and miR-155), have been mentioned, denoting the importance that the treatment should be adjusted to the genetic properties of the patient to increase the effectiveness as well as to decrease the appearance of secondary neoplasms [7, 17].

3. Molecular biological factors related to the development of leukemias

The evolution of AML is affected by the way in which leukemic cells change the tumor microenvironment in their favor, generating a niche that promotes their survival and drug resistance [4]. In this scenario, the presence of T lymphocytes is useful for the recognition and elimination of AML cells, being a factor to consider for therapies that take advantage of this interaction [13].

One target is CD123, the IL-3 receptor, expressed on AML leukemic stem cells. Although CD123-targeted therapies are in early stages, they represent a potential avenue for treatment [12]. Immune checkpoint inhibitors (ICIs), such as those targeting PD-1/PD-L1 and CTLA4, are being explored in AML due to their success in other cancers, given that AML blasts can evade the immune response by depleting T and NK cells, in addition to producing reactive oxygen species (ROS) that contributes to their apoptosis [4, 13]. Specifically, regulatory T cells (Tregs) show a high degree of immunosuppression in the BM of patients, complicating the function of effector T cells [13].

Anti-CD33 CAR-T-supported therapies have demonstrated preclinical effectiveness in AML cells, although toxicity in myeloid cells presents drawbacks. In relapsed B-cell acute lymphoblastic leukemia (B-ALL), CD19-targeted CAR-T therapies have achieved remission rates of 90% [6, 18]. Leukemia-specific neoantigens originating from leukemia mutations manifest in malignant clones and may be unique targets for precision therapies [19]. T cells are crucial in the regulation of tumor growth, although they lack Fcy receptors, which restricts their recruitment through traditional antibodies [20].

4. Immunological therapies for disease treatment

CAR T-cell therapy has shown great effectiveness in leukemias such as childhood B-ALL, with treatments such as CAR-T directed against the CD19 marker (e.g., Kymriah) demonstrating remission rates of 81% within three months. However, its effectiveness may be limited by loss of antigens on tumor cells and depletion of modified T cells [1, 3, 15, 21]. Dual CARs that simultaneously attack two targets, such as CD19 and CD22, are being developed, which could raise cure rates in patients with ALL [22].

In the case of AML, three main approaches have been developed in recent decades: recruitment of T cells by T-cell-capturing antibodies, genetic engineering of CAR-T, and reactivation of endogenous T cells by immune checkpoint inhibitors [19]. CAR-T development has been hampered due to the lack of specific antigens that allow safe treatment [3]; many targets such as CD33 are also present on healthy hematopoietic cells, leading to adverse effects. However, CAR-T directed against CD123 has demonstrated preclinical antileukemic activity, albeit with concerns about its toxicity towards normal HSPCs [1, 12, 13,]. A recent hypothesis posits CD33 deletion in healthy HSPCs, which would allow the use of anti-CD33 CAR-T without compromising normal tissue, which could be combined with allogeneic transplants of modified HSPCs offering an option for patients unresponsive to conventional therapies [23]. The CD33 knockdown strategy in healthy HSPCs has shown normal engraftment and differentiation in mouse models, and in a preclinical study with rhesus macaques normal myeloid functions were observed, in other tests complete remissions were seen in patients with AML and Blastic plasmacytoid dendritic cell neoplasm (BPDCN) with low doses of MB-102, without dose-limiting toxic effects [5, 13, 22].

Monoclonal antibodies, especially in the form of antibody-drug conjugates (ADCs), allow targeted delivery of cytotoxic drugs to tumor cells. A notable example is gemtuzumab ozogamicin, in which the anti-CD33 antibody is combined with calyceamicin to target CD33-positive leukemic cells, showing potent antitumor effects and minimizing damage to healthy tissues [1, 5, 24]. Other monoclonal antibodies, such as those directed against CD47 and CD123, have also shown clinical activity in trials in patients with refractory AML [1, 12, 13].

Immune checkpoint inhibitors, including anti-PD-1 antibodies such as nivolumab and pembrolizumab, and anti-CTLA-4 antibodies such as ipilimumab, work by blocking signals that inhibit the immune response against tumor cells. Although these treatments have shown success in solid tumors, their use in leukemias is still experimental. In AML, their study is focused on improving the immune response and addressing resistance in combination with other immunotherapeutics, especially in adult patients [2, 12, 13, 24].

Another immunotherapeutic strategy under development is CAR-NK cells, which combine the specificity of CARs with the innate activity of natural killer (NK) cells. CAR-NK cells overcome some of the limitations of CAR-T cells, such as the risk of cytokine release syndrome and graft-versus-host disease (GVHD), allowing their allogeneic use. These cells have been modified to target specific antigens, such as CD33 in AML, and have shown significant clinical responses in studies, with no serious adverse effects [15, 18, 25].

Stem cell transplantation remains an important curative option for patients with relapsed or refractory leukemias, especially in the case of AML, where allogeneic transplantation (allo-SCT) provides long-term disease control. This strategy benefits from minimal residual disease monitoring to reduce relapse rates, although there are significant risks of complications. CD33 deletion in allogeneic HSPCs, in combination with targeted CAR-T, has been proposed as a strategy to improve outcomes in patients with AML [11, 12, 22, 23].

Preclinical treatments for ALL include approaches targeting specific gene expression profiles and molecules involved in disease progression. In patients with ALL who have BCR-ABL-like expression profiles and carry gene fusions such as EBF1-PDGFB or NUP214-ABL1, the use of imatinib, an inhibitor of both Abelson tyrosine kinase (ABL) and PDGFB, is being evaluated [7]. In T-cell ALL, other genes such as BDR4 and BCL2 have been identified, which are overexpressed and related to MYC promotion and resistance to apoptosis. These genes have been postulated as therapeutic targets by NOTCH1, BDR4 and BCL2 inhibitors administered simultaneously [7].

T γ and δ T cells combine adaptive responses and rapid innate-like reactions, valuable in the early phase of immune reactions. These cells have the ability to recognize tumor cells without classical presentation by the major histocompatibility complex (MHC), which positions them as a key component for the immune response in situations where adaptive immunity is compromised, as occurs in recovery after haploidentical HSCT depleted of $\alpha\beta$T cells and CD19 B cells. This ability to reconstitute in patients with depleted HSCT suggests significant translational therapeutic potential, especially in acute leukemias [26].

Allogeneic hematopoietic progenitor transplantation (allo-HCT) represents an option with survival benefits superior to conventional chemotherapy in high-risk ALL patients, as it prolongs survival and reduces relapse rates compared to standard treatments [11]. This type of transplantation can be performed with progenitors from various sources, such as BM, peripheral blood (PB), and cord blood. In pediatric patients, BM is preferred due to its lower incidence of chronic adverse effects such as graft-versus-host disease (GVHD) and lower risk of long-term mortality compared to PB [27]. Nevertheless, the success of allogeneic HSCT can be hampered by disease relapse, this being the main cause of transplant failure [28]. In transplantation procedures, when siblings are used as matched donors, histocompatibility typing is performed to ensure compatibility, and a conditioning regimen based on busulfan (BU) and cyclophosphamide (CY) is administered. This BU regimen is adjusted according to the patient's weight and administered in specific doses, while CY is administered in the days prior to transplantation [18]. During the post-transplant phase, all patients receive strict isolation care and parenteral nutritional support, with anticonvulsant prophylaxis via phenytoin to prevent BU-induced seizures [18].

Asparaginase (L-ASA) is another essential component in the treatment of ALL, due to its ability to hydrolyze L-asparagine into aspartic acid and ammonium, thus depriving leukemic cells of this amino acid necessary for their proliferation. There are different forms of asparaginase on the market, such as that derived from Escherichia coli, Erwinia chrysanthemi, and pegylated (PEG-ASP). Dosing varies according to the type of L-ASA and the treatment protocol; for example, in low-risk pediatric patients, a less intensive strategy with L-ASA is used in induction and reinduction phases, whereas in high-risk patients, PEG-ASP is added in intensifications and reinductions [29]. Protocols for adolescents and young adults are inspired by pediatric regimens, with adjustments in asparaginase dosage depending on the age group and patient risk [29].

Blinatumomab is a bispecific antibody designed to activate T cells by targeting them against CD3 antigen and CD19 antigen on B cells, thereby promoting T cell cytotoxicity against leukemic B cells [2 ,30]. This approach has been effective in childhood ALL, increasing event-free survival and reducing the risk of relapse, particularly when used in combination with immune checkpoint inhibitors such as PD-1 blockade, which potentiates T-cell activity by removing inhibitory signals [20, 31 ,32].

Inotuzumab ozogamicin is a humanized monoclonal antibody targeting CD22, which upon binding internalizes and releases a potent toxin, calicheamicin, which induces apoptosis in leukemic cells. Its use, along with the mini-hyper-CVD regimen, a lower intensity chemotherapy protocol, has shown positive results. This regimen includes cyclophosphamide, dexamethasone, vincristine, methotrexate, and cytarabine in alternating cycles, with administration of inotuzumab ozogamicin on day 3 of the first cycles, adjusting the dose in each cycle to reduce toxicities while maintaining therapeutic effectiveness [33].

The therapeutic landscape for ALL and AML, based on immunotherapy and transplantation, highlights the move towards more personalized and less toxic treatments that maximize specificity and effectiveness in killing leukemic cells while minimizing the impact on healthy tissues and HSPC [1, 2, 5, 6].

5. Adversities in immunological therapies for leukemias

Important challenges remain, such as the identification of specific biomarkers to personalize treatments and improve efficacy without increasing side effects. Resistance to immunotherapy and the frequency of relapse in some patients remain barriers, highlighting the need for studies that optimize these therapies in each of the different types of leukemias [1, 2, 3, 6, 7].

In AML, patients usually have a high leukemic cell burden with low frequency of cell division, which limits the efficacy of cell cycle-specific drugs such as cytarabine; in contrast, daunorubicin, although it can target cells at different stages, has a narrow therapeutic margin, increasing toxicity [34]. T-cell-based immunotherapy has been shown to be effective in treating AML; however, in certain situations, leukemic cells generate evasion mechanisms such as antigen loss, decreased antigen exposure due to gene regulation, inhibition of T-cell activation through PD-L1, and mechanisms to avoid apoptosis [35]. The reduced mutational burden in AML also restricts the efficacy of tactics based on immune checkpoint inhibitors, as the lack of neoantigens hinders the immune system from efficiently detecting and attacking leukemic cells [36]. Additionally, although CAR-T treatments have shown progress, they can cause severe adverse effects such as hypogammaglobulinemia, infections, and neurological symptoms [22].

Issues such as hypersensitivity, thrombosis and hemorrhagic problems can commonly occur during treatment of ALL with L-ASA. L-ASA can also cause pancreatitis, hepatic and neurological toxicity, in addition to hyperglycemia; further complicating patient management and can be aggravated by interactions with other drugs, such as vincristine,

glucocorticoids and methotrexate, among others [29]. With regard to decreasing minimal residual disease in B-ALL, blinatumomab, a bispecific antibody that stimulates T cells against the CD19 antigen, has proven its effectiveness and safety, making it possible in certain situations for patients to undergo allogeneic HSC transfer without delay [30, 31].

6. Conclusions

Science and genetics are two important fields that will help us to overcome the difficulties of immunological treatments against leukemias and thanks to them there are already treatment options that today help many people to face this disease.

We must remember that acute lymphoblastic leukemia (ALL) is more common in children and adolescents and occurs more frequently between 2 and 5 years of age while acute myeloid leukemia (AML) is more common in adults and the average age of diagnosis of this leukemia is 69 years of age and with a higher incidence in men than in women.

- The immune system plays an important role against leukemia through T lymphocytes, NK cells and dentritic cells that will identify and eliminate leukemic cells.
- Therapeutic targets such as CD123 and specific neoantigens allow us to carry out more targeted treatments.
- CAR-T cell therapies are showing very promising results in preclinical studies and trials.
- The use of genetically modified hematopoietic stem cells to create a system of targeted therapies is being examined.
- In acute lymphoblastic leukemia (ALL), immunotherapy was shown to be effective as a therapy for this leukemia, especially with bispecific antibodies like blinatumomab, which will improve the ability to destroy carcinogenic cells by T-cells.
- Intensive chemotherapy, immunotherapy and allogeneic stem cell transplants are largely responsible for the increase in rates of survival.
- Inotuzumab ozogamicin is expanding the therapy options for patients who present a more persistent disease.
- It was found that γ and δ T cells which can recognize tumor cells, expanding the possibilities for new treatments.
- Similarly, genetic engineering platforms that modify T cells are opening up to new treatment possibilities.

However, in acute lymphoblastic leukemia (ALL), there will be some side effects from the administration of asparagine, and these can cause serious complications that will require specialized care.

As research progresses, it will be important to continue looking for new treatments and also to update or improve those currently available to guarantee effective and safe treatment for patients.

Compliance with ethical standards

Disclosure of conflict of interest

Authors have no conflicts of interest to declare.

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