Iranian Journal of Blood & Cancer

Iran J Blood Cancer, 2025, 17(3), 79-95
https://ijbc.ir

Review

The Immune Microenvironment in Acute Myeloid Leukemia: Mechanisms of Immune Evasion and Emerging Therapeutic Strategies

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Citation Kumar Singh V, Singh Matreja P, Singh S, Awasthi S. The Immune Microenvironment in Acute Myeloid Leukemia: Mechanisms of Immune Evasion and Emerging Therapeutic Strategies. Iran J Blood Cancer. 2025 Sep 30;17(3): 44-60.

doi 0

Article info:
Received: 21 July 2025
Accepted: 11 Sep 2025
Published: 30 Sep 2025

Keywords:
Acute Myeloid Leukemia
Hematological malignancies
Cytogenetics

Abstract

Acute Myeloid Leukemia (AML), a diverse type of blood cancer, is characterized by the unchecked multiplication of myeloid precursor cells within a disrupted bone marrow microenvironment (BMM). Leukemic blasts alter the BMM to create a leukemia niche, promoting immunological evasion and disease development. High relapse rates highlight the need for novel therapeutic approaches, even if chemotherapy is still the cornerstone of treatment. AML cells use many strategies to avoid immune identification, such as suppressing anti-leukemic immune responses and upregulating immune checkpoints. Immunotherapies like checkpoint inhibitors that target these pathways have shown encouraging promise. The intricate relationships between AML and the immunological milieu are examined in this review, with a focus on immune evasion, treatment resistance, and innovative immunotherapeutic strategies to improve anti-leukemic immunity.

1. INTRODUCTION

AML is a heterogeneous type of blood cancer that develops from transforming myeloid precursor cells within a disrupted BMM (1). Leukemogenesis is distinguished by the unregulated clonal expansion of malignant leukemic blasts, which shed their ability to differentiate correctly at numerous phases of maturation. Current insights indicate a two-way relationship among leukemic blasts and the BMM, with leukemic cells transforming the microenvironment into a niche that supports leukemia, while the modified BMM promotes disease advancement (2,3). In adults, AML represents the most prevalent leukemia, while in children it ranks as the second most commonly diagnosed type (4). Various factors influence patient survival, such as age and the existence of cytogenetic or molecular genetic dysfunctions (5). Although chemotherapy is the standard treatment method for most cases of AML and can lead to complete remission, most patients eventually relapse, highlighting the urgent need for new therapeutic strategies (5,6).

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[DOI: 10.61882/ijbc.17.3.79]

Consequently, a deeper comprehension of the immune regulatory mechanisms and tumor microenvironment has resulted in new treatment approaches for patients with AML. It is well known that in blood-related malignancies such as AML, the immune defense can recognize and eradicate tumor cells (7). Nonetheless, AML blasts utilize a variety of immune evasion tactics to avoid host immune reactions and escape destruction by the immune system (8). As a result, focusing on these co-inhibitory molecules—whether as a standalone treatment or in conjunction with other therapies—has shown considerable efficacy in AML by bolstering anti-leukemic immune responses (9,10).

This review aims to deliver a comprehensive examination of the immune microenvironment in AML, highlighting its impact on disease advancement, resistance to treatment, and new immunotherapeutic approaches. It also investigates the various approaches used by leukemia cells evading the immune response. This review aims to help develop more efficacious and personalized treatment methods for AML by elucidating these complex interactions.

2. Bone marrow microenvironment in blood cancers

The BMM is extremely crucial for controlling hematopoiesis. The self-renewing hematopoietic stem cells (HSCs) in the bone marrow (BM) are carried up by specialized niche cells, such as megakaryocytes, mesenchymal stromal cells, osteoblasts, endothelial cells, macrophages, sympathetic nerve fibers, and non-myelinating Schwann cells (**Figure 1**) (11). HSCs are mainly situated in perivascular niches in proximity to sinusoidal vessels, considering that prominent progenitor niches are found close to sinusoids, arterioles, or the endosteum (12). Thanks to progress in single-cell technologies, the gene expression profile of osteoblast, perivascular, and vascular populations in mouse BM has been thoroughly identified out, revealing significant cellular diversity within the niche under steady state conditions. Additionally, the origin of cells of pro-hematopoietic elements in the homeostatic BM environment have been recognized (11). Complementary studies in mice have further defined the various cellular subtypes within BM stroma, creating a detailed atlas of stromal cell populations (13). These investigations have pinpointed various subsets of stromal cells that express unique hematopoietic regulatory genes, such as fibroblastic and osteoblastic subgroups, and have delineated various pathways of osteoblast differentiation.

Under stress-inducing situations such as chemotherapy, the BM niche undergoes significant remodelling. Research

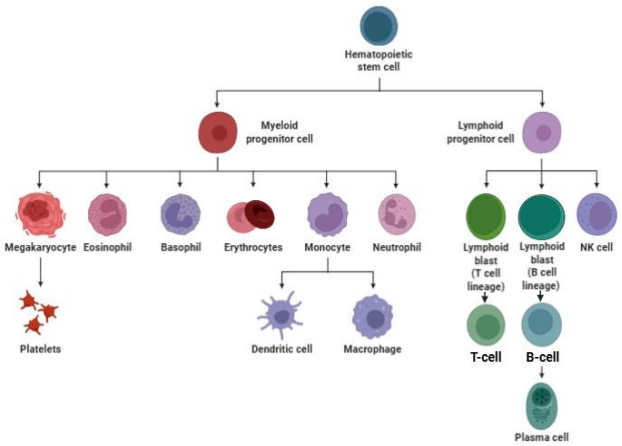

Figure 1. Illustration of mechanism of hematopoiesis.

with mice showed that perivascular mesenchymal cells exhibited a tendency to move toward adipogenic differentiation, as indicated by the transactivation of adipogenic genes and the inactivation of osteogenic genes. In addition, changes in the dissemination of pro-hematopoietic components were observed, along with a reduction in the magnitudes of vascular δ-like Notch ligands Dll4 and Dll1. It is worth mentioning that the lack of vascular Dll4 resulted in an early activation of a myeloid transcriptional program in HSCs. The results underscore the BM niche's dynamic qualities and its responsiveness to stress (11).

The BM niche is crucial to the onset, advancement, and treatment resistance of hematological malignancies, as it enables interactions between cancerous or potentially cancerous cells and their surrounding environment (14). Studies conducted with mice have demonstrated that modifications in cells environment correlate with myeloid neoplasms and changes in genetics which could lead to disorders bear a resemblance to myelodysplastic syndrome (MDS) or myeloproliferative neoplasms (MPNs). For instance, the scarcity of Dicer1 in osteoprogenitors gives rise MDS, and studies with BM transplantation have exhibited that the environment of BM can influence disease progression by enhancing the expression of stress related response genes and inflammatory cytokines (15). Analogously, gene Rarg, which encodes retinoic acid receptor γ, can be knocked out to create a myeloproliferative-like disorder in mice. Signaling of tumor necrosis factor (TNF) within the BM niche activates this condition (16). Age-related changes result in a proinflammatory BMM, increasing the likelihood of dysplasia and myeloid neoplasms. The age-related revolutionization in the niche of HSC leads to an excess of proinflammatory cytokines, which further encourages the

[DOI: 10.61882/ijbc.17.3.79]

excessive multiplication of myeloid cells and the expandment of progenitor cells with clonal hematopoiesis (CH) related changes, thereby commencing disease onset (17). When inflammation occurs in the BM niche, it disrupts hematopoiesis and requires HSCs to acclimatize to a high-stress environment marked by expanded adipogenic potential and dysfunctional sympathetic nerve activity (18,19). It is crucial to emphasize that research has demonstrated a significant reduction of sympathetic nerve fibers, nestin-expressing mesenchymal stem cells (MSCs), and Schwann cells in the BM of people with MPNs, as well as in mice with HSCs expressing the human JAK2-V617F mutation (20). It is important to note that sympathetic nerves undergo apoptosis due to the generation of interleukin-1β (IL-1β) by nestin-expressing niche cells when JAK2 mutations are present, which further disrupts BM homeostasis.

In MPNs, distinctive BM environment and HSC sequences have been recognized, impacting disease pathogenesis and resulting in diverse therapeutic responses, even in cases caused by the exact CH oncogenic mutation (21). Additionally, TET2 loss or mutation hinders MSC function in the BM, leading to a faster progression of myeloid malignancies (22). Comparable changes have been noted in the stem cell niche when ASXL1 mutations are present (23). Moreover, the age-related transformation of the BM stroma provides a selective benefit for DNMT3A-mutant clones, in part because of the guiding influence of TNF signaling (24,25).

Malignant cells and their released factors, such as exosomes, within the BM niche influence MSC function and alter their microenvironment to support leukemic cell survival. The atypical rise in myeloid cells leads to the excessive generation of proinflammatory cytokines by hematopoietic cells, whether they are mutated or non-mutated, adopting a proinflammatory phenotype (26). A downregulation of the chemokine CXCL12, which enables malignant HSCs to dominate their normal counterparts, is among the earliest inflammation-driven alterations in BM MSCs. This phenomenon is frequently seen in MPNs, acute lymphoid leukemia (ALL), AML, and chronic lymphocytic leukemia (CLL) (27,28).

Cytokines and growth elements, including bone morphogenetic proteins (BMPs), platelet-derived growth factor (PDGF), thrombopoietin, and CCL3, influence the proinflammatory BMM. These are released by either genetically changed hematopoietic cells or reprogrammed environmental cells. These elements promote the increase of osteoblastic cells, MSCs, and fibroblastic cells in myeloid malignancies (29). Research by Schepers et al. indicates that MPNs change the BM environment, as remodelled myeloid cells encourage MSCs to enhance the generation of osteoblastic lineage cells with altered functions. These cells accumulate in the BM cavity, contributing to both inflammation and myelofibrosis. In chronic myeloid leukemia (CML), the leukemic microenvironment produces elevated levels of BMP2 and BMP4, aiding in the persistence and self-renewal of leukemic progenitors (30). Within the MDS context, BM MSCs obtained from patients exhibit elevated apoptosis rates and a higher output of proinflammatory cytokines such as IL-6, IL-1β, and TNF (31). According to Medyouf et al., human MDS cells can reconfigure BM MSCs, which may assist in the process of disease implantation and progression *in vivo*. Similarly, MSCs obtained from AML patients show genetic abnormalities and an improper regulation of cytokine secretion. Genetic fate-mapping studies have identified MSCs that express leptin receptors as crucial contributors to fibrosis in primary myelofibrosis. In the BM niche, these cells enlarge through PDGF receptor-α signaling (32). BM fibrosis, which characterizes myelofibrosis, is driven by GLI1+ MSCs that differentiate into myofibroblasts. In murine models, CXCL4 boosts the relocation and development of GLI1+ MSCs, and focusing on these cells has been shown to reduce fibrosis, culminating in their capacity as therapeutic targets (29).

Along with immune regulation, leukemias acclimate to and make the most of the vascular endothelial niches found in the BM. In murine models, factors such as CXCL12, Notch, and E-selectin signaling pathways drive this adaptation of the endothelium. These promote interactions between leukemia and vessels that play a role in vascular dysfunction (33,34). Furthermore, hypoxia and increased angiogenesis are important characteristics of hematologic malignancies (35). Hematopoietic cells that are malignant show a heightened rate of oxygen utilization and generate pro-angiogenic factors such as vascular endothelial growth factor A (VEGF-A) and different interleukins. These factors subsequently promote the production of placental growth component by BM MSCs. This process results in the creation of new blood vessels, which boosts the production of the generation of oxygen and nutrients and acts as a reservoir for elements that support the survival of malignant cells. Ultimately, the reprogramming of the niche of BM aids in the survival and multiplication of leukemia cells while contributing to their chemotherapy resistance.

3. AML: Overview and Clinical Characteristics

AML is a clonal disorder of the hematopoietic system that originates from genetic and molecular aberrations affecting

[DOI: 10.61882/ijbc.17.3.79]

normal hematopoietic stem cells. As a consequence of the alterations, blasts—immature myeloid cells—are produced that multiplicate uncontrollably and accumulate in the BM (36). These abnormal cells outcompete and take the place of normal hematopoietic progenitors, leading to characteristic cytopenias and leukocytosis (37). According to recent epidemiological data, AML has an incidence rate of 4.3 cases per 100,000 people, with the median age at diagnosis being 68 years. In the United States, the estimated 5-year overall survival rate is around 24% (38).

Like most cancers, AML develops from the accumulation of somatic driver mutations and secondary genetic alterations. Currently, cytogenetic analysis and next-generation sequencing (NGS) are used for diagnosing AML (39). Among the mutated genes linked to leukemogenesis, those involved in signaling pathways and protein kinase activation, such as FLT3, are essential for the abnormal activation and multiplication of leukemic blasts (40). FLT3 mutations are indispensable in the development of AML, principally because they frequently interact with other genetic changes, particularly NPM1 mutations. NPM1-mutated AML is usually linked to a positive prognosis; however, the presence of both FLT3 and NPM1 mutations changes risk stratification and correlates with early relapse and worse clinical outcomes (41,42). A further significant category of driver mutations encompasses genes that control epigenetic alterations, including DNA methylation and chromatin remodeling. Mutations in DNMT3A, for example, hinder the differentiation of HSCs, whereas mutations in TET2 disrupt normal myeloid differentiation (42). Moreover, significant cytogenetic abnormalities—such as chromosomal translocations, gene amplifications, insertions, and deletions—play essential role in the development of AML and are essential markers for risk classification and treatment strategy formulation (43).

AML is a heterogeneous cancer type that primarily affects the BM and PB, but can also impact extramedullary tissues in certain cases (44). Pancytopenia, characterized by anemia, thrombocytopenia, and neutropenia, arises from bone marrow failure due to the infiltration of leukemic blasts. Clinically, AML often presents with symptoms such as weakness, fatigue, recurrent infections, and hemostatic problems, including bruising, ecchymosis, and nosebleeds (45). In AML, fever can arise from two different mechanisms: it may be a neoplastic fever resulting from the leukemic proliferation itself, or it may occur due to neutropenia, which makes patients more susceptible to recurrent infections. Moreover, extramedullary manifestations can involve lymphadenopathy, hepatosplenomegaly, and bone lesions (46).

Coagulation abnormalities, whether hemorrhagic or thrombotic, rank among the most severe complications of AML and are responsible for approximately 7% of mortality in these cases (47). Coagulation dysfunction can arise in different AML subtypes, but it is most frequently linked to acute promyelocytic leukemia (APL) (48). Leukostasis, a medical emergency characterized by symptomatic hyperleukocytosis, is another important clinical manifestation that occurs in 10 to 20% of AML patients. Leukostasis can lead to pathological alterations in different organs; the central nervous system (CNS) and lungs, however, are impacted the most, with complications that can be deadly (49). The diagnosis of AML is made when blasts constitute at least 20% of the BM or PB, with the exception of certain cases where particular cytogenetic findings are sufficient for confirmation (50). Bone marrow aspiration is a crucial diagnostic procedure assessed through various methods, such as morphological evaluation, flow cytometry for classifying AML subtypes, cytogenetic analysis to find chromosomal abnormalities, and NGS for detecting gene mutations (51).

The main objective of AML treatment is to attain disease remission, which is defined by the lack of detectable blasts and molecular markers. The treatment method adheres to a proven protocol and is divided into two primary phases: induction and consolidation therapy (52). As the primary treatment, intensive induction chemotherapy aims to reduce leukemic blasts in the bone marrow to below 5%. The standard treatment for patients who qualify for intensive therapy is a regimen that combines Cytarabine for seven days with Daunorubicin or Idarubicin for three days. This is known as the "7 + 3 protocol." Since the 1970s, this treatment has led to disease remission in over half of patients across all age groups (53). To establish the suitable treatment plan, especially for elderly patients who might not withstand aggressive chemotherapy, a comprehensive initial evaluation is crucial. Other treatment options, including hypomethylating agents in combination with Venetoclax or low-dose Cytarabine, have demonstrated encouraging outcomes regarding overall survival and quality of life enhancement (54,55). Following induction therapy, consolidation treatment is administered to reinforce remission achieved during the initial phase. Consolidation treatment is given after induction therapy to bolster the remission achieved in the initial phase (56), Patients may acquire high-dose chemotherapy or pass through bone marrow transplantation with the aim of curing the disease (57).

Although remission can be achieved in AML, relapse is frequent due to drug-resistant leukemic clones, which leads

[DOI: 10.61882/ijbc.17.3.79]

to complications and death related to the disease. Approximately 24% is the overall 5-year survival rate, which remains low (58). Regrettably, the addition of re-induction regimens to targeted therapies like tyrosine kinase inhibitors has not led to significant improvements in patients' long-term survival outcomes (59).

A unique and well-defined subtype of acute myeloid leukemia (AML), acknowledged by the WHO as AML with PML-RARA (60), is acute promyelocytic leukemia (APL), which is also mentioned to as AML-M3 in the French-American-British (FAB) classification system (61). APL is distinct from other AML subtypes due to its specific histological and clinical features, including the presence of Auer rods and a high propensity for disseminated intravascular coagulation (62). Therapeutic approaches for APL also differ from those used for standard AML. Most AML cases are treated using the 7 + 3 induction regimen (which involves cytarabine alongside daunorubicin or idarubicin), but for low-risk APL patients, induction therapy consists of arsenic trioxide and all-trans retinoic acid. This approach results in high remission rates and excellent overall survival outcomes (63). As a result, the primary research focus remains on improving therapeutic strategies for non-APL AML cases.

A considerable advancement in the comprehension of different facets of AML physiology has occurred in recent years, especially regarding the function of BM niches. A range of innovative treatment methods have been explored to target specific niche cell populations, components of the extracellular matrix, various adhesion molecules, and growth factors secreted by niche cells. These strategies aim to modify the BMM in order to disrupt the initiation and progression of leukemia, with the ultimate goal of improving clinical outcomes (2,64).

4. The immune microenvironment in AML

The BMM is crucial for the initiation and progression of AML, with recent research shedding light on its transcriptional changes during transformation (42,65). Changes in stroma have been observed in the leukemic bone marrow niche, characterized by impaired mesenchymal cell differentiation and reduced expression of genes involved in hematopoiesis (13). AML disrupts both osteogenic and adipogenic differentiation pathways within the stroma of BM, adversely affecting hematopoiesis and overall tissue function. A groundbreaking study utilizing single-cell RNA sequencing combined with co-detection by indexing (CODEX) generated a spatially resolved multi-omic map of human BM. This work revealed distinct spatial microenvironments and previously unrecognized heterogeneity among human MSCs. Additionally, the study emphasized the spatial association between MSCs and leukemic blasts in AML patients (66,67).

Extensive investigations of the endothelial portion in the BM microenvironment of AML have uncovered a significant increase in vascular permeability, alongside molecular changes in endothelial cells (68). Patients with elevated nitric oxide levels who underwent induction chemotherapy exhibited vascular dysfunctions in the BM, which are linked to a poor prognosis. Furthermore, AML blasts alter the bone marrow niche by secreting exosomes that increase DKK1 expression, thereby undermining the ability of mesenchymal stromal progenitors to differentiate into osteoblasts. In addition, these explosions reduce the expression of HSC-supporting elements like IGF1, CXCL12, KITL and in stromal cells of BM (69). Research has shown that leukemic cells can modify the tumor microenvironment (TME) by generating a range of immunosuppressive enzymes, including arginase, CD73, CD39 and indoleamine-2,3-dioxygenase-1 (70–73). Additionally, it has been pointed out that AML cells residing in the BM niche rely on cytokines and soluble components generated by MSCs and AML cells as well, such as CXCL12, IL-10, IL-4, and IL-1β, transforming growth factor-β (TGFβ). This paracrine signaling pathway fosters immune tolerance and facilitates blast growth by involving neighboring cells in the TME (74,75).

Metabolic rewiring's role in the onset, progression, and relapse of AML has been thoroughly investigated (76). Hypoxia and competition for nutrients are crucial elements that promote immunosuppression in the TME. The growth of tumors and the activation of immune subsets cause an increase in glycolytic metabolism, which raises lactate production and leads to acidosis within the TME. The effector functions of various subsets of immune cells, comprising monocytes, regulatory T (Treg) cells, NK-cells, macrophages, dendritic cells, and effector T-cells, are directly impeded by this acidic environment (77). Numerous investigations have shown that individuals undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) display elevated oxidative markers and an imbalanced antioxidant status in their serum (78). Cells that have dysregulated reactive oxygen species (ROS) levels show significant oxidative DNA damage, which could jeopardize antileukemic immune surveillance (79).

Transformations in the immune microenvironment are closely linked to modifications in the BM niche. It is essential to comprehend the phenotypes, functions, and developmental trajectories of immune cells in the AML microenvironment in order to reveal mechanisms of

[DOI: 10.61882/ijbc.17.3.79]

immune evasion and enhance immunotherapy responses. Changes at the junction of T-cells and leukemic blasts can result in decreased immune recognition, playing a role in post-transplant relapse in up to 40% of cases. After allo-HSCT, signals that are costimulatory and mandatory for T-cell switching on are consistently interrupted. Leukemic cells specifically downregulate activators like CD11A and B7-H3 while upregulating inhibitory ligands like PVRL2, PD-L1, and CD80 (80,81). The immunophenotypic changes of T-cells during relapse must be noted as being comparable to those seen in leukemic blasts (80,82). There is mounting evidence indicating that the shared articulation of several inhibitory checkpoint receptors on T-cells acquired from donors correlates with relapse after transplantation. Leukemia antigen-specific T-cells show an increased expression of TIM-3 and LAG-3 in HLA-matched transplants (83). In line with this, transplant recipients showed that PD-1hiTIM-3+ T-cells demonstrated indications of productive exhaustion and rose in frequency prior to clinical relapse, highlighting a robust correlation between the quantity of these cells and leukemia relapse (84). Furthermore, the bone marrow of relapsed AML patients exhibits elevated levels of $CD8^{+}PD\text{-}1^{+}TIM\text{-}3^{+}$ and $PD\text{-}1^{+}LAG\text{-}3^{+}$ T-cell populations (85). Upon diagnosing relapsed AML, the BM exhibits an increased proportion of Treg cells and a greater incidence of PD-1+ and OX40+ T-cells (85). Single-cell analyses have revealed that myeloid cells resulting from AML-associated differentiation possess immunosuppressive characteristics (86). In addition, immune profiling in AML has identified various immunosuppressive subsets of dendritic cells and macrophages, accompanied by reduced and dysfunctional T-cell and NK-cell populations, along with regulatory T-cells exhibiting abnormal developmental pathways (87). While NK cells can contribute to the suppression of AML in its initial stages, disease advancement is linked to diminished perforin expression and the depletion of immature NK-cell subsets, driven by the dysregulation of a microRNA essential for NK-cell maturation (88). In the bone marrow immune microenvironment of both adult and pediatric AML patients, an increase in dysfunctional B-cells has been observed (notably atypical memory B cells), granzyme-producing CD8+ progenitors of depleted T-cells, and Treg cells, while T-cell clonal expansion is diminished, all occurring against a backdrop of heightened inflammation (89). Research into pediatric AML has uncovered unique gene expression patterns linked to relapse, diagnosis, and complete remission, which are associated with survival outcomes (90). At diagnosis, among a cohort of pediatric patients, those who later experienced relapse exhibited a greater depletion of T-cells and a reduced presence of inflammatory macrophages compared to those who maintained sustained remission. These findings underscore the complexity of immune dysfunction in AML and its progression with the disease, highlighting the diverse immune cell populations present in the bone marrow. Understanding how immune populations are reprogrammed is crucial for interpreting the unique immune landscapes of patients, as these may influence the success of immunotherapies. In this regard, research on PD-1 blockade therapy has revealed significant variability in T-cell subsets, with responders showing an expansion of the CD8+ T-cell population, further supporting the potential of targeted immune therapies in AML treatment (91).

5. Mechanisms of Immune Evasion in AML

In AML, numerous mechanisms aid in immune evasion (**Figure 2**) (92). The exact contribution of each mechanism to the promotion of leukemia immune tolerance, their functioning in PB compared to BM (the primary tumor site), and the effects of AML treatment and genetics on them require further exploration.

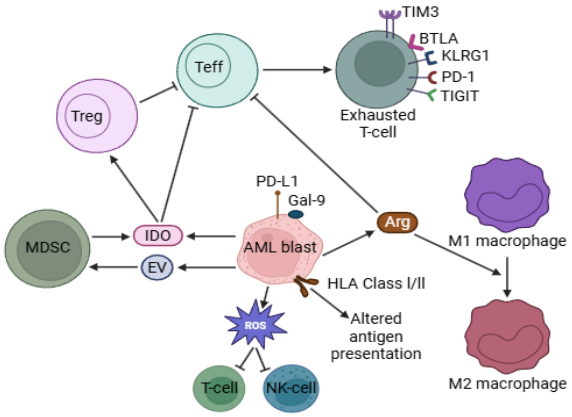

Figure 2. The dysfunctional immune landscape associated with acute myeloid leukemia.

5.1. Changes in Antigen Presentation

After allo-HSCT, leukemia blasts exhibit significant immunoediting in response to selective immune pressure (93). Additionally, the downregulation of HLA class II molecules through epigenetic mechanisms has been observed in various donor transplant scenarios (80,81). Mouse models have shown that leukemia antigen presentation by immature antigen-presenting cells or splenic CD8α+ dendritic cells can induce T-cell tolerance, including deletional and CD8+ T-cell tolerance (95). Furthermore,

[DOI: 10.61882/ijbc.17.3.79]

recent research has linked impaired plasmacytoid dendritic cell differentiation to the persistence of measurable residual disease post-AML treatment, which is associated with poorer survival outcomes (96).

5.2. T and NK-cells

T-cell exsistence at the tumor site is crucial for immune identification and destruction of AML cells, as well as for the effectiveness of therapies that utilize this mechanism. Compared to healthy controls, AML patients show a similar number of T-cells in the BM and increased levels of total and CD8+ PB T-cells (85). Higher proportions of lymphocytes and T lymphocytes in the BM have been associated with enhanced treatment responses and better survival rates (97), while a robust recovery of lymphocytes after chemotherapy is linked to a reduced relapse risk (98). It has been shown that higher expressions of CD8+ and CD3+ T-cells in the BM, when combined with a hypomethylating agent (HMA), are predictive of positive responses to the checkpoint inhibitor nivolumab (99).

Research using mouse models of AML has shown that with disease progression, CD8+ T-cells expressing the PD-1 checkpoint inhibitory receptor (CIR) and Tregs increase at the tumor site, suggesting the potential of targeting the PD-L1/PD-1 pathway to reduce Treg levels (100). Additionally, a mouse model revealed that exhausted CD8+ T-cells co-expressing PD-1 and TIM3 could have their cytotoxic function restored through combined checkpoint inhibition (101). In AML patients, phenotypic and gene expression analyses of CD8+ and CD4+ T-cells at diagnosis showed an abnormal activation profile and alterations in genes crucial for immunologic synapse formation (102). Despite reduced IFN-γ production by CD4+ T-cells, AML T-cells remain functionally competent in cytokine generation and proliferation, with PD-1 upregulation indicating a shift towards effector memory cells (103). Multiple studies, including ours, have shown that the frequency of T-cells co-expressing CIRs in AML patients is higher than in healthy controls, with this frequency increasing as the disease progresses (85,92). Smaller-scale studies have suggested that CD8+ T-cells with CIR expression are functionally impaired and can predict relapse in AML patients (104). While the general cytokine expression in CD8+ T-cells of AML patients is similar to healthy controls, senescent and exhausted T-cells with distinct cytokine profiles have been identified, with reversible transcriptional signatures observed in patients responding to chemotherapy (92). A recent study found that in favorable-risk AML, BM CD8+ T-cells contribute to leukemia stem cell (LSC) expansion, while in adverse-risk AML, LSC expansion is independent of CD8+ T-cells (105). The frequency of PD-L1+ AML cells varies across studies, ranging from 18% to over 50%, and PD-L1 expression increases upon relapse, especially in acute monocytic leukemia, which is associated with poor prognosis (85,106). Additionally, PD-L1 expression and other co-signaling ligands are upregulated on AML blasts during post-alloHSCT relapse, alongside corresponding T-cell alterations (80). Exposure to IFN-γ results in increased PD-L1 expression in leukemia blasts (107) and primary AML blasts rapidly upregulate PD-L1 as an adaptive resistance mechanism against immune therapies that activate T-cells (108).

Leukemic blasts are crucial for the modulation of T-cell responses. When T-cells are exposed to AML blasts *in vitro*, they experience apoptosis, reduced proliferation, and diminished costimulatory molecule expression. Cells of monocytic leukemia generate ROS, which lead to the death of T cells and NK cells *via* apoptosis that depends on poly(ADP-ribose) polymerase-1 (PARP-1) (109). When exposed to AML blasts *in vitro*, NK cell cytotoxicity and effector functions are diminished. At the time of diagnosis, patients with AML already exhibit functionally compromised NK-cells, marked by a decrease in activating receptors and an increase in the inhibitory receptor NKG2A. Upon remission, these phenotypic and functional variations in NK-cells can be partially reversed; however, they persist in patients who do not react to therapy (110). Furthermore, it has been shown that the leukemia-associated fusion proteins PML-RARα and AML1-ETO specifically diminish the display of CD48 on AML cells. CD48 serves as the ligand for the NK cell receptor 2B4 (CD244), and this decrease impacts the cytotoxic function of NK cells (111).

5.3. Immunosuppressive microenvironment

Studies conducted on both mice and humans indicate that Tregs have a considerable impact on weakening immune responses in AML (112). In AML patients, Tregs in the PB and BM are elevated and have a stronger immunosuppressive effect on Teffs compared to normal Tregs. Additionally, their levels show minimal changes with chemotherapy (85). Moreover, elevated Treg levels correlate with worse AML outcomes (113).

Myeloid-derived suppressor cells (MDSCs) are elevated in AML patients and contribute to T-cell tolerance through various mechanisms, including the expression of PD-L1 and VISTA, indoleamine 2,3-dioxygenase (IDO) activity, and the production of reactive oxygen species (ROS), peroxynitrate, arginase, and cytokines like TGF-β and IL-10 (9). AML cells promote MDSC development by releasing extracellular

[DOI: 10.61882/ijbc.17.3.79]

vesicles (EVs) containing the oncoprotein MUC1, which increases c-myc expression and drives MDSC proliferation (114). In high-risk myelodysplastic syndromes (MDS), Tregs and MDSCs are positively correlated, suggesting their role in disease progression, a correlation not seen in low-risk MDS (115).

Enzymes produced by AML blasts contribute to the creation of a suppressive microenvironment. The expression of IDO in AML blasts, which catalyzes the rate-limiting step of tryptophan degradation via the kynurenine pathway, is linked to shorter relapse-free survival and overall survival times (116). The depletion of tryptophan and accumulation of its metabolites suppress T-effector (Teff) cell proliferation, promote T-cell apoptosis, and induce Tregs (117). Arginase II, elevated in AML patients, inhibits myeloid-monocytic differentiation, reduces T-cell proliferation, and drives monocyte polarization towards a suppressive M2-like phenotype (71). Studies in animal models of monocytic AML have shown that arginase I enhances leukemia aggressiveness by promoting tissue infiltration and T-cell suppression through the LILRB4 receptor signaling pathway (118).

6. Targeting the Immune Microenvironment in AML Therapy

Since leukemic blasts exploit the immune microenvironment to avoid detection by the immune system, numerous novel therapeutic approaches are being created to focus on these immune-evasive mechanisms and reinstate anti-leukemic immune responses.

6.1. Checkpoints inhibitors (CPIs)

In AML, immune evasion is mediated by checkpoint molecules such as CTLA-4 and PD-1 on immune cells, and Tim-3 and PD-L1 on leukemic blasts. Immune checkpoint inhibitors (CPIs) targeting PD-1 (e.g., Nivolumab, Pembrolizumab) and CTLA-4 (e.g., Ipilimumab) have shown efficacy in solid tumors (119). Currently, the safety and feasibility of these CPIs are being investigated in several ongoing phase I/II clinical trials (120).

In relapsed hematologic malignancies post-allogeneic HSCT, the CTLA-4 inhibitor Ipilimumab has shown limited clinical benefit, with Graft versus Malignancy (GvM) responses observed in under 10% of cases. While Ipilimumab did not induce Graft versus Host Disease (GvHD) in initial trials, immune-related adverse events occurred in 14% of responders (121). Another study reported immune-related toxicities in 10 of 28 patients, including one death and four dose-limiting GvHD cases, with complete remission achieved in 4 out of 12 patients (122,123). Similarly, a retrospective analysis of clinical trials using PD-1/PD-L1 inhibitors in AML and high-risk MDS revealed dose-limiting immune toxicities (38). The efficacy and safety of CTLA-4 blockade appear dose-dependent and influenced by AML histological subtypes. Notably, durable remissions were seen in extramedullary AML, including leukemia cutis, alongside mild GvHD (122). In progressive AML, the anti-PD-1 antibody CT-011 showed limited anti-leukemic activity but was well tolerated as monotherapy (124). The varying response to checkpoint inhibitors in AML may reflect heterogeneous checkpoint expression profiles (125), with murine studies showing increased co-expression of checkpoint molecules and effector cell exhaustion as the disease progresses (101).

To address the limited efficacy of CPI monotherapy in AML, combination strategies are under investigation. Ongoing clinical trials (NCT03417154, NCT02464657, NCT02768792) are assessing the effectiveness of CPIs with chemotherapy. A Phase II study adding Nivolumab three weeks after standard chemotherapy (anthracycline and cytarabine) in newly diagnosed AML and high-risk MDS patients demonstrated feasibility and efficacy, though 6 out of 44 patients experienced grade 3 or 4 immune-related toxicities (126). Additionally, a Phase I/II trial showed that Nivolumab combined with the hypomethylating agent Azacytidine is both effective and well-tolerated in relapsed, high-risk AML cases (127).

In order for CPI therapy to work, it is crucial that effector lymphocytes react appropriately. In the context of AML, though, this reactivity diminishes in the immunosuppressive leukemic BMM, that probably obstructs treatment effectiveness. Furthermore, the usually low tumor mutation burden of AML, acknowledged as a predictive marker for CPI response, may impede T-cell recognition (128). Considering the highly immunosuppressive environment and the generally low baseline expression of immune checkpoints in AML (128,129), HMAs that boost anti-leukemic immune responses through increased cellular reactivity and upregulation of checkpoint molecule expression (130) could potentially enhance CPI treatment outcomes. Ongoing studies are examining the use of combined checkpoint blockade approaches aimed at PD-(L)1, CTLA-4, or Tim-3 in conjunction with HMA therapy (NCT03066648, NCT02530463). Among these, the Tim-3/Galectin-9 axis stands out as especially promising for targeting, given its involvement in LSC self-renewal (131) and its upregulation in AML therapy-resistant cases (104).

Considering that various studies have identified distinct shared-expression sequences of immune checkpoints that

[DOI: 10.61882/ijbc.17.3.79]

hold prognostic significance (85,131), combination or dual checkpoint inhibition may represent a promising strategy for tackling immune system avoidance in AML. In a pediatric patient with refractory AML, initial symptom improvement was observed without adverse effects after simultaneous obstruction of CTLA-4 and PD-L1 combined with HMA treatment. Nonetheless, despite this initial response, the treatment did not end up preventing the disease's progression. Further studies are necessary to evaluate the clinical effectiveness of this combined therapy strategy in pediatric AML (132).

6.2. Cell-based therapy

Cellular therapies for leukemia were initially inspired by the potent T-cell-mediated anti-leukemic effects seen following allogeneic HSCT (133). A 20-year single-centre study on haploidentical T-cell infusion in relapsed AML patients showed moderate feasibility, though immune-related toxicities, particularly severe GvHD, limited its clinical applicability (134).

Preclinical studies have demonstrated that CAR T-cells engineered to target CD123 or CD33 exhibit anti-leukemic activity against AML cells (135,136). Ongoing early-phase clinical trials are evaluating anti-CD33 CAR T-cells in pediatric and adolescent patients with relapsed or refractory AML (NCT03971799). Moreover, bispecific CAR T-cells targeting both CD123 and CD33 have shown effectiveness in eliminating leukemic blasts and LSCs *in vivo* (137). Despite these advances, CAR T-cell therapy remains challenged by significant T-cell-mediated toxicities, including cytokine release syndrome and an increased risk of GvHD (138). On the other hand, NK-cells present a safer option because of their MHC-independent activity, which leads to reduced cytokine release and a lower risk of GvHD. Consequently, research is being conducted into the viability of adoptive NK-cell therapy as a promising, inexpensive, and easily accessible off-the-shelf treatment option (139).

Various NK cell–based immunotherapies have been explored for AML. Preclinical models showed that CD123-targeting CAR-engineered NK cells demonstrated anti-leukemic activity and safety (140). In a pediatric case of relapsed AML post-HSCT, adoptive transfer of cytokine-induced allogeneic NK cells proved effective and well tolerated (141), with further evaluation underway in Phase 1/2 trials (NCT03068819, NCT01898793). However, a Phase I clinical trial of CD33-directed CAR-NK cells reported good tolerability but limited therapeutic efficacy (142).

Adoptive transfer of purified allogeneic haploidentical KIR-HLA mismatched NK cells following low-dose immunosuppression and IL-2 administration has shown encouraging response rates with minimal toxicity and no GvHD, making it a potential consolidation therapy for AML across age groups (143,144). However, efficacy appears dose-dependent, as a higher dose (29×10^6/kg) was effective, while a lower dose (12.5×10^6/kg) was not in pediatric patients (143,145). In contrast, lower doses ($1–5 \times 10^6$/kg) have proven effective and feasible in elderly AML patients (146), suggesting that other factors like NK-cell purification and cytokine stimulation may influence therapeutic success (147).

6.3. Antibody-based therapy

While true tumor-specific antigens are rare, leukemia-associated markers such as CD33 and CD123—commonly expressed on AML blasts and LSCs—have been investigated as therapeutic targets, despite their presence on some healthy HSCs (148). Traditional monoclonal antibody therapies targeting these antigens have shown limited clinical efficacy (149). Consequently, recent efforts have shifted toward engineered antibodies, including antibody–drug conjugates (ADCs) and Fc-optimized antibodies designed to enhance CD16 binding and improve ADCC.

Initial clinical trials of the CD33-targeting ADC Gemtuzumab ozogamicin (GO), linked to the cytotoxic agent calicheamicin, demonstrated its feasibility and effectiveness in treating pediatric patients with relapsed or refractory (R/R) AML (150). The U.S. FDA approved GO for R/R AML in adults with CD33-positive AML and for children aged two years and above. Similarly, the European Medicines Agency (EMA) authorized its use in patients over 15 years with newly diagnosed AML, following positive results from the ALFA-0701 trial (NCT00927498) (151). Recently, the FDA expanded GO's indication to include children as young as one month with newly diagnosed CD33-positive AML, based on data from the AAML0531 study (NCT00372593) (152). Additionally, preliminary results from a phase I trial of a CD123-targeting ADC linked to an alkylating agent in relapsed or refractory AML showed both safety and clinical efficacy (153).

CLL-1 is predominantly expressed on AML blasts and leukemia stem cells (LSCs), but not on hematopoietic stem cells (HSCs), making it a promising therapeutic target that preserves hematopoietic regeneration (154,155). Both *in vitro* and *in vivo* models have shown strong anti-leukemic effects of CLL-1-targeting ADCs and the bispecific T-cell-engaging antibody CLL1-CD3. The latter demonstrated greater efficacy than CD33-targeted therapies by specifically sparing HSCs (156).

[DOI: 10.61882/ijbc.17.3.79]

Phase I trial results of a dual-affinity anti-CD123-CD3 antibody in patients with refractory or relapsed AML and MDS showed T-cell-mediated anti-leukemic effects and an acceptable safety profile, with manageable cytokine release syndrome (mainly grades 1 and 2) as a persistent adverse effect (157). Animal studies using an AML-monkey model indicated that a bispecific T-cell engager with lower CD3 affinity resulted in reduced cytokine release compared to its high-affinity CD3 counterpart (158).

Preclinical studies showed that the Fc-engineered CD123 antibody CSL362, designed to enhance NK-cell affinity, effectively mediated NK-cell cytotoxicity against AML blasts and LSCs (159). However, CSL362 showed limited anti-leukemic efficacy in phase I/II trials, likely due to NK-cell depletion in heavily treated advanced AML patients (160). Proposals suggest that bi- and tri-specific NK-cell engagers targeting CD123 and CD33, such as CD33-CD16, CD123-CD33-CD16, and CD123-IL15-CD16, could enhance antibody-dependent cellular cytotoxicity (ADCC) (161). Additionally, HMAs may improve NK-mediated anti-leukemic responses by counteracting immune evasion and enhancing NK-receptor activation, boosting NKG2D-mediated NK activation (162). A novel strategy combining immune checkpoint inhibitors (CPIs) and bispecific T-cell engagers (BiTEs) aims to revitalize exhausted T- and NK-cells, indicating that combining immune therapies with NK-cell-engaging treatments could be a promising future direction, though further research is needed.

Tetra-specific antibodies have been developed for solid tumor treatment, incorporating CD16 linked to IL-15 to activate NK cells. These antibodies are fused with single-chain variable fragments (scFvs) targeting cancer-associated antigens (163). Due to the genetic and morphological diversity of AML blasts, this multi-specific approach could offer a promising antibody-based treatment for AML, allowing precise targeting of leukemic blasts based on their unique surface marker profiles.

6.4. Cytokines and Immune-Modulating Factors in Therapeutic Intervention

Researchers have looked into cytokine-based therapies, both as standalone treatments and alongside other immunogenic anti-leukemic methods, since various pro-inflammatory cytokines like IL-12, IL-15, IL-18, and IL-21 have been demonstrated to enhance leukemia-specific immunogenicity (164).

To enhance anti-leukemic immunogenicity, NK-cells can be modified into memory-like NK-cells *via ex vivo* stimulation using a combination of IL-12, IL-15, and IL-18. When contrasted to their native/non-activated counterparts, these memory-like cells demonstrate increased leukemia-targeting activity (165). These cytokines enhance the sensitivity of IL-2 receptors on NK cells, thereby improving their functionality. Because of the elevated levels of the IL-2 receptor alpha-chain (IL-2R/CD25) on Treg cells, which sequesters IL-2 and restricts its availability for NK-cell stimulation, IL-2 mainly activates immunosuppressive Tregs instead of NK-cells (147). This led to the outcome that various studies evaluating IL-2 as a single treatment did not accomplish the expected anti-leukemic effectiveness (166). A meta-analysis examining the effects of IL-2 as a sole treatment found no significant advantage compared to no intervention in terms of overall or disease-free survival rates (167).

To improve the efficacy of allogeneic NK-cell-based therapy, an IL-2 diphtheria toxin fusion protein targeting Treg cells expressing IL-2R (CD25) was administered before NK-cell infusion and IL-2, successfully restoring NK-cell mediated anti-leukemic immunity (147). Phase I/II trials showed that substituting IL-2 with recombinant IL-15 enhanced NK-cell expansion *in vivo* and resulted in promising remission rates in patients with advanced AML (NCT01385423, NCT02395822) (168). These studies also revealed that subcutaneous administration was linked to cytokine release syndrome and neurotoxicity, while intravenous delivery was not (169). Additionally, a phase I trial is ongoing to evaluate the safety and feasibility of IL-21-expanded NK-cells *ex vivo* (170).

N-803, a super-agonist of IL-15/IL-15Ra, is designed to replicate the immune-stimulating effects of antigen-presenting cells. These cells convey a trans-presenting form of IL-15, which is bound to IL-15Ra, to NK-cells and cytotoxic T-cells via the common IL-2/IL-15 alpha/beta receptor (169). N-803 showed promise as a single-agent treatment in early clinical trials, demonstrating both tolerability and effectiveness in managing leukemic disease. In more recent times, studies have been evaluating the use of N-803 alongside NK-cell infusion (NCT01898793, NCT02782546). Type I interferons are believed to have both anti-leukemic and pro-immunogenic effects on cancers. However, their effectiveness as a standalone treatment is limited (171).

Due to the complex nature of the leukemic BMM, many immunosuppressive factors play a role in restricting anti-leukemic immune responses. Therapeutic agents that reduce lymphocyte suppression caused by leukemia may counteract these constraints. In this context, focusing on inhibitory-mediators like IDO 2,3 or TGF-β could provide promising strategies to address leukemia-associated immune evasion and improve the effectiveness of cell-based therapies

[DOI: 10.61882/ijbc.17.3.79]

in AML. It has been demonstrated that blocking IDO 2,3 can improve immune regulation mediated by T and NK cells, while also averting the differentiation of Treg cells (172). In a similar vein, blocking PGE2 has shown to enhance anti-leukemic immune responses (173). Therefore, the integration of these immunoregulatory approaches could boost the efficacy of cell-based therapies.

Studies have underscored the role of TGF-β in dampening immune responses across different cancers, and inhibiting TGF-β has been demonstrated to bolster lymphocyte-mediated immune reactions against tumors, especially in non-hematologic cancers. Preclinical studies have shown that blocking TGF-β maintains NK-cell anti-leukemic activity in the presence of high pathological levels of TGF-β (174).

In certain subtypes of AML, phases of both cell bound and soluble HLA-G are heightened, which is thought to be an effective means of reestablishing immune responses due to HLA-G's regulatory influence on NK, T, and dendritic cells. Moreover, by binding to NKG2A, HLA-E inhibits the activity of NK cells, which makes it a potential target for therapy. Nonetheless, preclinical and clinical data assessing the practicality of these strategies are limited or have yet to be investigated.

6.5. Vaccines

Vaccination is gaining attention as a potential treatment to improve anti-leukemic immune surveillance, with two main approaches: (i) targeting leukemia-associated antigens and (ii) using dendritic cells to present antigens. Peptide-based vaccines targeting the Wilms tumor gene (WT-1), created with a natural or modified 9-mer WT1 peptide and montanide ISA51 adjuvant, have shown good tolerability and induced specific cytotoxic T-cell responses (175). This led to significant reductions in leukemic burden and minimal residual disease (MRD) markers in 60% of AML patients after consolidation therapy. The WT-1 vaccine, administered intracutaneously, may serve as an effective second-line maintenance therapy to enhance the graft-versus-leukemia (GvL) effect after hematopoietic stem cell transplantation (HSCT) (176). In phase I/II trials, the multivalent WT-1 vaccine galinpepimut-S administered to AML patients in complete remission elicited a targeted immune response, improved survival, and showed no significant toxicity. A phase III trial (NCT04229979) has been initiated to further assess its efficacy and safety (177).

Dendritic cells (DCs), as powerful antigen-presenting cells, are ideal for use as cellular adjuvants in therapeutic vaccination. A phase II trial (NCT00965224) showed that WT1-mRNA-loaded DCs could effectively stimulate antigen-specific T-cell responses, potentially preventing or delaying relapse after chemotherapy (178). Additionally, autologous DCs electroporated with mRNA for human telomerase reverse transcriptase (hTERT) demonstrated safety and feasibility, contributing to extended recurrence-free survival in AML patients in complete remission (179). Another promising approach involves using a hybridoma of leukemic cells and DCs derived from the patient as a personalized vaccine, which has been shown to promote T-cell expansion and targeted anti-leukemic effects, reducing relapse risk in pre-treated AML patients (180).

A cryogel vaccine, combining immunostimulatory CpG-oligodeoxynucleotide and GM-CSF with leukemia-associated antigens, effectively triggered anti-leukemic immunity by activating dendritic cells (DCs). When used in combination with chemotherapy, this vaccine prevented leukemic engraftment and successfully eradicated established leukemia in mice with AML (181). Notably, the cryogel vaccine also cleared leukemia in the absence of predefined antigens, likely due to the accumulation of apoptotic AML blasts that provided sufficient antigens to enhance immune responses mediated by DCs (181).

Considering the difficulties associated with clinical trials of new immunotherapeutic strategies and the complex immunosuppressive characteristics of the leukemic microenvironment, combining cellular and non-cellular immunotherapies may provide a more powerful approach to effectively combat leukemic immune evasion.

7. CONCLUSION

Acute Myeloid Leukemia (AML) remains a formidable challenge due to its aggressive nature, high relapse rates, and complex interactions with the bone marrow microenvironment (BMM). Leukemic blasts actively reshape the BMM into a leukemia-supportive niche, fostering immune evasion and disease progression. While chemotherapy remains the standard treatment, its limitations highlight the urgent need for novel therapeutic strategies.

The immune microenvironment plays a crucial role in AML pathophysiology, with leukemic cells exploiting various immune evasion mechanisms, including immune checkpoint upregulation and suppression of anti-leukemic responses. Recent advances in immunotherapy, such as checkpoint inhibitors and other targeted approaches, offer promising avenues for overcoming immune resistance and enhancing treatment efficacy.

A deeper understanding of the intricate crosstalk between AML cells and the immune microenvironment is essential for developing more effective, personalized treatment

[DOI: 10.61882/ijbc.17.3.79]

strategies. Future research should focus on refining immunotherapeutic interventions, identifying predictive biomarkers, and optimizing combination therapies to improve patient outcomes. Utilizing the capacities of the immune system can lead to more long-lasting and targeted treatments for managing AML.

Acknowledgment

The authors would like to thank all the people who contributed to the writing of this article.

Conflict of interest

The authors declared no conflict of interest.

Funding

No fund was received.

Ethical statement

Not applicable.

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[DOI: 10.61882/ijbc.17.3.79]