Cytotoxic Immune Cell Dysfunction in Leukemia

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Leukemia is a malignancy of the bone marrow and blood resulting from the abnormal differentiation of hematopoietic stem cells (HSCs). There are four main types of leukemia including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL). While chemotherapy and radiation have been conventional forms of treatment for leukemia, these therapies increase infection susceptibility, adverse side effects and immune cell inactivation. Immunotherapies are becoming promising treatment options for leukemia, with targeted therapies opening the door to a variety of options that maximize cancer cell neutralization and minimize off-target host tissue damage. In order to generate efficacious targeted therapies, it is crucial to pinpoint specific immune cell populations that are impaired to reverse this exhaustion.

Keywords: leukemia ; natural killer (NK) cells ; CD8+ T Cells ; cancer

1. Introduction

Although approximately 14 billion dollars are spent annually on leukemia care alone in the US, 5-year patient mortality rates have remained consistent over the past 30 years at ~35%[1][2]. In 2022, a projected 60,650 new cases will be diagnosed, with an estimated 24,000 patient deaths[3]. These alarmingly high statistics present a pressing need to develop new therapies in order to improve treatment strategies and subsequent patient recovery[4]. Treatment for leukemia patients can vary depending on the type of leukemia, the age of the patient and stage of cancer development but will often include chemotherapy and radiation therapy[5][6]. While effective in some cases, both chemotherapy and radiation therapy are aggressive forms of treatment that can cause toxic side effects, leading to significant damage in not only the target cells, but also healthy tissues [7][8]. Recently, several forms of immunotherapy options for leukemia have been marketed including targeted antibodies, adoptive cell therapy and immunomodulators [9]. In contrast to the non-specific cell destruction induced by chemotherapy and radiation, immunotherapy offers a targeted, antigen-specific treatment option that utilizes the patient's own immune system to combat cancer proliferation [10][11]. In order to generate efficacious immunotherapies for leukemia, establishing the mechanisms by which leukemic cells evade immune detection is crucial.

1.1. Leukemia

Leukemia is characterized as multiple malignancies that affect the blood and bone marrow and is often the result of both genetic and environmental factors [12]. During leukemia, excess proliferation of leukemic cells from hematopoietic stem cells (HSCs) occurs, resulting in a crowding out of developing immune cells and decreased production of important lymphoid or myeloid cells. Leukemic cells are also capable of eventually infiltrating from the bone marrow into the bloodstream and have the potential to infect systemically, affecting both the peripheral and central nervous systems [13].

There are four main types of leukemia including chronic myeloid leukemia (CML), acute myeloid leukemia (AML), acute lymphoblastic/lymphocytic leukemia (ALL) and chronic lymphocytic leukemia (CLL). While these four types of leukemia are the most common and will be the primary topics of discussion, it is important to note that there are several other rare forms of leukemia as well, including prolymphocytic leukemia (PLL), large granular lymphocytic leukemia (LGL) and hairy cell leukemia (HCL). The four more common types of leukemia are separated not only by acute vs. chronic presentation, but also by the specific lineage the leukemia originates from [12]. Acute leukemia is typically more severe as cancerous cells in this state proliferate rapidly, preventing blood stem cell maturation, while chronic leukemia progresses more slowly and prevents development of blood cells from HSCs. Myeloid leukemia develops from potential myeloid cells that would typically differentiate into red blood cells, platelets or white blood cells including granulocytes or monocytes such as neutrophils, basophils and eosinophils. In contrast, lymphocytic leukemia develops from potential lymphocytic cells that would, under normal circumstances, differentiate into T cells, B cells and NK cells [14].

Conventional modalities of treatment for leukemia include chemotherapy, targeted therapy, and radiation treatment with possible bone marrow transplantation (BMT) if needed. Although these treatment models have shown various success rates in the past, patients are subject to multiple adverse side effects, increased risk of infection and the possibility of leukemic relapse. Patients with a previous history of chemotherapy or radiation therapy also have an increased risk of developing secondary leukemia, which is often difficult to treat and has a poor prognosis [14].

While overall 5-year survival rates for leukemia remain high, treatment of relapsed leukemia remains a major obstacle as these patients often present with chemoresistance and a significantly impaired immune system [15][16]. CAR-T cell therapies have been explored for use in leukemia and have shown some success in recognition of cancer cells, but this form of treatment is often coupled with severe side effects including encephalopathy, coagulopathy, hypoxia, and neurotoxicity [17][18][19][20]. With the success of targeting the immune system for improved patient recovery, less toxic alternatives to CAR-T therapies are being actively explored. Natural killer cell dysfunction has been well characterized in leukemia and shown to play a role in both disease severity and progression [21][22]. NK-cell based immunotherapies in the form of adoptive transfer and immune checkpoint inhibitors (ICIs) have shown promise for treatment of both primary and relapsed leukemic presentation [23][24][25]. This review highlights dysfunction of these two cytotoxic immune cells during leukemia, how this dysfunction varies depending on patient presentation and how targeting specific elements of these immune cells could prevent or treat the exhausted phenotypes observed.

1.1.1. Myeloid Leukemia

Acute myeloid leukemia (AML) often occurs due to chromosomal abnormalities or mutations in the genes NPM1, CEPBA, RUNX1 and FLT3 and is characterized by an over-accumulation of abnormal cells called myeloblasts. AML occurs more frequently in older populations with the average age of diagnosis reported as ~65 years of age and the current 5-year survival rate stands at 28% [26]. This reportedly older age of diagnosis presents complications as some physicians may have reservations using traditional, rigorous treatment methods for elderly and subsequently more at-risk patients [26]. Treatment phases for AML typically includes induction therapy to destroy the leukemia cells followed by consolidation to kill any remaining cancer cells. Anthracycline is often the standard of care for AML, which is a drug that increases the patient's risk of congestive heart failure. Even though rigorous treatment methods are used, 40–60% of patients relapse after initial treatment, requiring subsequent follow-up therapy in the form of hematopoietic stem cell transplants (HSCTs), additional chemotherapy, or targeted therapies [27]. Several forms of immunotherapy are currently under investigation for treatment of AML, including bispecific antibodies, CAR-T cell therapy and NK cell therapy [28].

Chronic myeloid leukemia occurs as the result of a translocation occurring between chromosomes 9 and 22, causing an abnormal gene fusion of BCR-ABL1. This is a somatic rather than acquired mutation, meaning it can occur randomly and does not require genetic predisposition. This gene fusion causes uncontrolled cell division and blockage of apoptosis, resulting in excess production of abnormal cells from HSCs, resulting in CML [29]. In similarity to AML, CML primarily affects older populations, with over half of the diagnoses being above the age of 64 [29]. Additionally, it affects slightly more men than women and accounts for approximately 15% of leukemia cases nationwide [30][31].

In theory, the translocation mutation is an excellent target using tyrosine kinase inhibitors (TKIs); however, many patients fail to fully respond, with a decreased rate of recovery after each subsequent treatment [32]. Even though the majority of CML patients present with resistance and in some cases intolerance to TKIs such as nilotinib, dasatinib and bosutinib, this form of therapy remains mainstay for high-risk patients [33]. TKI treatment has been shown to have a direct effect on NK cell activity. Dasatinib has been shown to increase expression of both inhibitory and activating NK cell receptors, while Imatinib has been shown to play a primarily stimulatory role by upregulating expression of only activating receptors [34][35]. Research exploring alternative therapies for TKI-resistant CML patients has shown that NK cell transfusions have the capability to overcome this drug resistance in advanced stages of development [36][37]. Since TKIs have been identified as playing a role in regulating NK cell activity, future research focused on using TKIs in combination with checkpoint inhibitors that upregulate NK cells could prove beneficial for the improvement of treatment strategies.

1.1.2. Lymphocytic/Lymphoblastic Leukemia

Acute lymphocytic/lymphoblastic leukemia (ALL) is the most common form of leukemia in children and is caused by chromosomal changes such as translocations, insertions or deletions that lead to excess cell division [38]. The most common mutations that have been identified in ALL patients include translocations in BCR-ABL1, ETV6-RUNX1, TCF3-PBX1, and MLL-AFF1 with additional mutations occurring in PAX5 and IKZF1 [39]. ALL can be further categorized based on both the chromosomal and genetic mutations observed as well as the lymphocyte subtype affected (B cell lymphocytic/lymphoblastic leukemia vs. T cell lymphocytic/lymphoblastic leukemia). While 5-year survival rates for childhood ALL patients is an encouraging 87%, this survival rate significantly decreases following relapse, emphasizing

the need for treatment that returns the immune system to a more homeostatic state to prevent this relapse from occurring [40]. The current standard of treatment for pediatric ALL includes combination chemotherapy, and clinical trials are underway to determine effectiveness of combining chemotherapy with targeted monoclonal antibody treatment (blinatumomab) [41]. Since leukemia cells have the potential to spread to the brain and spinal cord, treatment often includes intrathecal chemotherapy. Stem cell transplants may also be performed if a pediatric patient does not respond well to conventional treatment [42].Continued investigation of targeted immunotherapy for ALL patients remains a priority to maximize patient recovery. ALL patients with systemic peripheral leukemia have been shown to express elevated levels of IL-15, which is involved in activation of NK cells. As NK cells have been shown to be capable of direct lysis of abnormal immature WBCs in these patients, NK cell transfusions from healthy donors show promise in improving patient prognoses [43].

Chronic lymphocytic leukemia (CLL) is the most common type of adult leukemia and while it can affect both sexes, occurs more frequently in men than women. CLL is thought to occur due to damage of genes involved in blood development and results in the production of abnormal cells that would typically differentiate into the B cell subset [44]. Several somatic mutations involved in development of CLL include ATM, TP53, RB1, BIRC3 and MYD88 as well as gene rearrangements of BCR-ABL [45]. B cell deficiency characterized by this form of leukemia causes patients to have a significantly increased risk of acquiring bacterial infections. Current first lines of treatment for CLL include chemotherapy in combination with monoclonal antibodies or other forms of targeted treatment; however, these forms of therapy are not always effective [46].

2. Cytotoxic Immune Cell Dysfunction in Leukemia

2.1. Immune Evasion in Leukemia

The immune system is adept at recognizing abnormal or foreign cell proliferation and eliminating it before it becomes a systemic issue. Therefore, cancer cells have had to adapt multiple mechanisms by which to evade immune cell recognition. Several ways cancer cells can do this that include antigenic modulation, inducing a tumor microenvironment, suppressing immune cell function and imitation of healthy tissues [47][48]. Due to the characteristically low mutational burden observed in leukemia patients, relatively low quantities of neoantigens are presented, resulting in minimal T cell activation [49]. In the context of NK cells, leukemia can also avoid recognition by manipulating the expression of activating and inhibitory ligands on their surface [50]. Upregulation of inhibitory ligands increases the probability that corresponding NK cell receptors will recognize this ligand and continue with circulation rather than marking the cell for apoptosis. In addition to upregulation of inhibitory receptors, cancer cells can also shed HLA molecules to avoid detection by T cells [51][52][53][54][55]. Downregulated expression of MICA/MICB receptors is another mechanism of tumor escape from NK cells, given these receptors interact via NKG2D to activate NK cell activity [56][57]. This mechanism of tumor resistance is indicative of a poor prognosis in patients with leukemia specifically. Another method of tumor escape from NK cell recognition involves NKp44 interactions via its ligands with proliferating cell nuclear antigen (PCNA) and HLA I, which have shown upregulation on cancerous cells [58]. NKp44 can act as an inhibitory or activating receptor depending on the ligand interactions involved, but interactions with PCNA or HLA I cause inhibition of NK cell activity [59].

In addition to upregulation of inhibitory receptor interactions, the tumor microenvironment can also actively suppress the immune response by secreting molecules such as transforming growth factor-β (TGF-β), which inhibits NK cell effector function and survival [60][61]. Secreted enzymes such as matrix metalloproteinases (MMPs), disintegrin and metalloproteinase (ADAM) also act to shed receptors from the surface of tumor cells, further impairing immune cell-mediated elimination of tumor cells [62].

2.2. Functional Impairment of CD8+ T-Cells in Leukemia

CD8+ T cell dysfunction has been characterized in multiple different types of cancers and has been identified as strongly correlated with poorer prognosis[63]. Immunotherapies targeting cytolytic T cell dysfunction has been a hot topic of research for the past several years, with a variety of options being tested including monoclonal antibodies, genetically engineered chimeric antigen receptor (CAR) T cells and adoptive transfer of this immune cell subset. Interestingly, research has been published which pinpoints CD8+ T cell activity to potentially play a role in progression of some forms of leukemia including AML. A study looking at the gene profiles of CD8+ T cells in 30 different AML patients showed that downregulated expression of genes associated with proliferation and differentiation was strongly correlated with improved patient prognosis[64]. Next, the researchers went on to look at the gene expression profiles of LSPCs (leukemia stem/progenitor cells) and found that there was significant upregulation of genes involved in proliferation and the cell cycle compared to the controls. To functionally explore the relevance of these upregulated genes and determine if there was a relationship between CD8+ T cells and LSPCs, the researchers performed co-cultures with these two cell types and found that the presence of CD8+ T cells actually induced expansion and proliferative capabilities of LSPCs, implicating a

maintenance role of leukemic cells. This unexpected discovery was shown to only hold true for more favorable-risk AML, with development of more aggressive forms primarily independent of CD8+ T cell expansion. Additional studies investigating this process in CML had similar findings and indicated that secretion of IFN-γ was at least partially implicated in this mechanism of resistance[65]. Collectively, these studies implicate the importance of identifying the risk level of CML/AML prior to beginning any form of treatment in order to ensure it will not exacerbate leukemic progression.

Research investigating T cell dysfunction in CLL patients identified the CD8+ T cell subset to display high surface expression of exhaustion associated markers including PD1, 2B4 (CD244) and CD160[66]. As indicated in patients with AML/CML, IFN-γ production by these immune cells was also enhanced and cytotoxic impairment appeared to be at least partially due to the inability of CD8+ T cells to undergo granzyme localization at the immunological synapse. This study implicates PD1, 2B4 (CD244) and CD160 as mediators of immunosuppression during CLL, identifying these markers as potential therapeutic targets of interest.

Another research study exploring the long-term effects of Ibrutinib (TKI) found that patients undergoing this form of treatment presented with progressively enhanced CD8+ T cell activity and a reduction in the characteristically exhausted phenotype seen[67]. Specifically, treatment with the TKI resulted in a downregulation of the PD-1 receptor on the CD8+ T cells, resulting in decreased suppression of this immune cell subset and improved proliferation. Alternatively, prior research investigating the effects of Ibrutinib on CD8+ T cell expansion found that this form of treatment actually impairs immune cell function during the first 6 months of treatment[68]. These studies implicate the importance of further researching the impact of various treatment options both short and long-term in order to effectively predict and combat potential negative side effects.

2.3. Functional Impairment of NK Cells in Leukemia

Research has shown that the leukemic microenvironment induces a decrease not only in the number of active NK cells, but also in the cytotoxic and degranulation capabilities of these innate immune cells [69]. A study observing lymphocyte population subsets in CML patients vs. healthy volunteers showed that $CD8^+$, $CD4^+$, $CD3^+$ T cell and B cell numbers remained consistent, while NK cell counts dropped significantly [69]. Patients in this study treated with imatinib, a TKI, did not see a significant improvement in either NK cell activation or degranulation capabilities, indicating a continuation of a suppressed microenvironment. A study looking at NK cell function in CLL established that NK cells had defective degranulation capabilities and were maintained in a primarily hyporesponsive state, while another study using AML patients showed not only reduced NK cell degranulation capabilities, but also upregulated inhibitory receptor expression and reduced TNF-α production by NK cells [70][71].

A study looking at NK cell activity in B- and T-ALL patients showed that numbers were significantly decreased in both the bone marrow and peripheral blood [72]. B-ALL NK cells were shown to have significantly decreased cytotoxic capabilities compared to NK cells from healthy donors when killing assays were employed with ALL sensitive leukemia cells, indicating an immunosuppressed phenotype. Further analysis showed that NK cells from B- and T-ALL patients were predominantly from the $CD56^{bright}$ subset, which is considered an immature precursor to the more cytotoxic $CD56^{dim}$ NK subset. This study implies that NK cell maturation and differentiation into more cytotoxic counterparts is impaired during leukemia. Suppressed NK cell activity has also been implicated in B- and T-lymphoid malignancies that present with *MYC* oncogenic abnormalities [73].

Mouse experiments comparing NK cell populations in healthy vs. *MYC*-activated leukemic and *MYC*-suppressed leukemic groups discovered that the group with *MYC*-activated oncogenes had drastically reduced NK cell numbers. When *MYC* was suppressed, NK cell populations were at nearly normal levels, indicating that NK cell suppression is *MYC*-dependent. Further downstream signaling pathways implicated to play a role in suppression include STAT1/2 and type 1 IFN, which are repressed by *MYC* overexpression. A study investigating NK cell dysfunction in AML used a RAG GC KO mouse model to show that when the mice were injected with leukemic blasts in combination with NK cells, there were significantly lower numbers and impaired capabilities of these NK cells 21 days after the transfusion [74]. Wild-type mice NK cells presented with higher percent perforin, granzyme B and IFN-γ expression. Flow cytometry staining of Ki62 (a marker of proliferation) on NK cells showed that NK cells in the leukemic environment had impaired proliferative capabilities.

Similar to previous studies, leukemia-treated mice presented with impaired NK cell maturation. microRNA miR-29b was noted as highly upregulated in NK cells from leukemia-treated mice and as this miRNA has been shown to regulate T cell activity via EOMEs and T-bet, knockdowns were performed on miR-29b and found to restore NK cell activity to heightened proliferative levels. While the mechanism behind regulation of NK cell activity in leukemia is not fully understood, it is likely that the leukemic microenvironment directly (secretion of IL-10 or TGF-β) or indirectly (overexpression of suppressive-associated genes) suppresses activity via multiple different mechanisms. Collectively, these findings suggest that NK cell

dysfunction is a major proponent of the leukemia microenvironment and studies focused on targeting specific receptors involved in NK-cell-suppressive effects could maximize immune function and patient survival.

3. Conclusion

Overall, cytotoxic immune cell exhaustion is a major proponent of the leukemic microenvironment. Research implicates that treating this exhaustion directly could be a way to train a patient's immune cells to naturally recognize and lyse the cancerous cells, but this form of treatment, especially in the context of CD8+ T cell therapies must be optimized in order to prevent treatment from potentially playing a synergistic role with leukemia stem cells depending on patient presentation. The future of treatment for Leukemia remains bright, but additional research is needed to determine ideal populations for this form of therapy.

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