Research in Molecular Medicine

Venetoclax in T-cell Acute Lymphoblastic Leukemia: The Impact of BCL-2 Inhibition on Treatment Efficacy

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Citation Tari K, Valizadeh Ardalan P, Abroun S. Venetoclax in T-cell Acute Lymphoblastic Leukemia: The Impact of BCL-2 Inhibition on Treatment Efficacy. Research in Molecular Medicine. 2023; 11(4):213-226. https://doi.org/10.32598/rmm.11.4.678.6

https://doi.org/10.32598/rmm.11.4.678.6

Article Type:
Review Paper

Article info:
Received: 05 Jul 2023
Revised: 10 Aug 2023
Accepted: 19 Sep 2023

Keywords:
Venetoclax, T-cell acute lymphoblastic leukemia (T-ALL), BCL-2, Apoptosis, Targeted therapy

ABSTRACT

T-cell acute lymphoblastic leukemia (T-ALL) is a rare and aggressive leukemia that targets T-cells, a subtype of white blood cells. Despite advancements in treatment, T-ALL continues to be a formidable disease to manage, characterized by high relapse rates and a dismal prognosis. Recent studies have underscored the promise of B-cell lymphoma 2 (BCL-2) inhibition as a treatment approach for T-ALL. Venetoclax, an innovative BCL-2 inhibitor, has demonstrated encouraging outcomes in preclinical investigations. Inhibition of BCL-2 with venetoclax constitutes a unique and promising therapeutic strategy for T-ALL, with improved treatment results and fewer adverse effects. As researchers persist in investigating the efficacy of venetoclax and other BCL-2 inhibitors, patients with T-ALL may soon access more effective and focused treatments. Recent advancements in the research and development of combination medicines and the discovery of novel biomarkers offer the potential for enhanced treatment outcomes with venetoclax. This paper thoroughly examines the present state of BCL-2 inhibition in T-ALL and underscores the promise of venetoclax as an innovative therapeutic approach, stressing the necessity for additional research to harness its potential fully.

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Introduction

T-cell acute lymphoblastic leukemia (T-ALL) is a rare and aggressive type of hematologic malignancy that impacts the blood and bone marrow. The primary hallmark is the atypical proliferation and accumulation of immature T cells. T-ALL constitutes roughly 25% of all acute lymphoblastic leukemia cases and is predominantly observed in children and young people, peaking in prevalence between the ages of 2 and 5 [1]. T-ALL constitutes approximately 12% to 15% of all newly diagnosed cases of ALL in pediatrics and is significant due to its distinct clinical and molecular characteristics. Historically, T-ALL's prognosis is worse than B-cell acute lymphoblastic leukemia B-(ALL)'s; however, new therapeutic developments have progressively improved event-free survival rates, surpassing 85% in numerous clinical trials. Moreover, recurrent disease presents significant treatment challenges, and a limited number of novel pharmaceuticals have been formulated for pediatric patients with resistant conditions [2].

At present, the etiology of T-ALL is still unclear. It is neither communicable nor hereditary; however, specific genetic alterations, commonly involving *NOTCH1* and *CDKN2A*, may be inherited, heightening vulnerability to T-ALL [3]. Mutations in epigenetic regulators are prevalent in T-ALL, complicating the disease's molecular landscape. The prognosis for T-ALL is affected by multiple factors, including cytogenetics and the existence of central nervous system (CNS) involvement at diagnosis. About 80% of relapses transpire within two years after diagnosis, underscoring the disease's aggressive characteristics [4].

The pathophysiology of T-ALL is intricate, encompassing various genetic and molecular processes. Progress in comprehending these pathways has resulted in the creation of targeted medicines and immunotherapeutic approaches, providing optimism for enhanced outcomes in T-ALL patients. Current research and clinical trials are investigating novel approaches to treat this disease, intending to enhance survival rates and quality of life for individuals afflicted by this aggressive condition [5].

B-cell lymphoma 2 (BCL-2) is a protein that regulates apoptosis or programmed cell death. BCL-2 is frequently overexpressed in cancer cells, such as those in T-ALL, resulting in the survival and proliferation of malignant cells. Inhibiting BCL-2 with agents such as venetoclax has demonstrated potential in treating T-ALL by reinstating apoptosis and triggering cell death in neoplastic cells [6]. Venetoclax is a highly selective inhibitor of BCL-2, sanctioned for the treatment of specific leukemia forms, including chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML) [7]. Recent studies have established the efficacy of venetoclax in treating T-ALL, yielding promising response rates and survival outcomes [8, 9].

Venetoclax has demonstrated encouraging response rates in preliminary research and clinical trials. Its therapeutic efficacy is ascribed to its capacity to induce apoptosis in BCL-2-dependent cells. The combination of venetoclax with additional medications, such as chemotherapy or targeted therapies, has enhanced response rates, particularly in high-risk patient populations. Preliminary studies indicate that venetoclax may prolong progression-free survival and overall survival in specific patient groups, especially those with BCL-2 overexpression and resistance to prior treatments. Nonetheless, its effectiveness may be affected by further mutations that provide resistance, and the ideal incorporation of venetoclax into current therapy protocols has to be conclusively established [10]. The combination of venetoclax with other novel agents is currently under investigation.

This article seeks to analyze the impact of venetoclax on T-ALL, emphasizing the significance of BCL-2 inhibition in enhancing therapy results. This paper aims to elucidate the mechanisms of BCL-2 inhibition and the clinical experience with venetoclax in T-ALL, thereby offering a thorough grasp of this therapeutic strategy's possible advantages and drawbacks.

Therapeutic Resistance in T-ALL

The conventional therapy for T-ALL consists of a rigorous multi-phase chemotherapy protocol encompassing induction, consolidation, and maintenance phases, frequently accompanied by CNS prophylaxis (Table 1). Despite these intensive therapies, approximately 20%–25% of patients experience recurrence, and the prognosis for relapsed T-ALL is typically unfavorable. Notwithstanding considerable progress in treatment, chemotherapy resistance continues to provide a substantial problem in the management of this disease and directly affects patient survival rates. Therapeutic resistance refers to the capacity of cancer cells to endure and multiply despite chemotherapy, resulting in disease recurrence and diminished treatment effectiveness [11].

A significant component in treatment resistance in T-ALL is the presence of genetic abnormalities in essential signaling pathways. Activating mutations in the *NOTCH1* gene in over 50% of T-ALL patients might enhance cell survival and proliferation, augmenting

Table 1. Common treatment methods for T-ALL

Treatment Approach	Mechanism of Action	Notes
Chemotherapy	Destroys rapidly dividing cells	Commonly used protocols include hyper-CVAD and UKALL
Targeted therapy (e.g. NOTCH1 inhibitors)	Targets specific genetic mutations, like *NOTCH1*, to block abnormal signaling	Effective in cases with *NOTCH1* mutations
Corticosteroids (e.g. prednisone)	Suppresses immune responses and inflammation	Often part of induction therapy to reduce leukemic burden
Tyrosine kinase inhibitors (e.g. dasatinib)	Blocks tyrosine kinase enzymes involved in cell growth signaling	Particularly useful in cases with *ABL1* and *FLT3* mutations
Immunotherapy (chimeric antigen receptor T-cell therapy)	Uses modified T-cells to attack leukemic cells	A promising option for relapsed or refractory T-ALL
Stem cell transplant (allogeneic)	Replaces diseased bone marrow with healthy donor stem cells	Often used after achieving remission through chemotherapy
Radiation therapy	Uses high-energy radiation to kill cancer cells in localized areas	Usually reserved for specific sites, such as the CNS

treatment resistance [12]. Mutations in the PTEN gene, which negatively regulates the PI3K/AKT pathway, may also increase cellular resistance to therapy [13]. Moreover, alterations in the expression of apoptosis-related genes, including the upregulation of antiapoptotic BCL-2 family proteins, contribute to the resistance of leukemia cells to programmed cell death, hence facilitating the survival of cancer cells in the presence of chemotherapeutic agents [14].

Besides genetic alterations, the tumor microenvironment is another crucial component in treatment resistance. Leukemic cells engaging with stromal cells in the bone marrow and other protected niches can insulate themselves from the adverse effects of chemotherapy. These connections can transmit survival signals to cancer cells, enhancing their medication resistance. Furthermore, the microenvironment might directly diminish the effectiveness of chemotherapeutic agents, resulting in heightened resistance among cancer cells [13].

A significant challenge in treating T-ALL is the intrinsic heterogeneity of cancer cells. The heterogeneity indicates that distinct cells within a tumor may have varied responses to different treatments. This cellular heterogeneity results in the development of therapy-resistant clones capable of repopulating following the first treatment, leading to disease recurrence. To tackle these issues, it is imperative to create novel and combinatorial therapeutic techniques. BCL-2 inhibitors, such as venetoclax, are novel strategies for addressing therapy resistance in T-ALL. These inhibitors can boost the sensitivity of cancer cells to chemotherapeutic agents and promote cell death by blocking antiapoptotic proteins [15]. Integrating targeted medicines, such as NOTCH1 or PI3K/AKT inhibitors, with conventional chemotherapy is a potential strategy. These techniques target molecular pathways linked to resistance and modify the tumor microenvironment to enhance therapeutic efficacy [11]. While these techniques necessitate validation and evaluation in clinical research, they have instilled significant optimism for enhancing treatment results in patients with therapy-resistant T-ALL.

A comprehensive understanding of therapeutic resistance processes and developing novel and combinatorial therapy strategies can enhance the therapeutic prognosis for patients with T-ALL and markedly elevate patient survival rates.

Importance of BCL-2 Protein in T-ALL

BCL-2 is a crucial regulator of the intrinsic apoptosis pathway, significantly influencing cell survival and death. The inhibition of apoptosis is a fundamental mechanism of cancer proliferation, with BCL-2 family members playing a pivotal role in controlling this process [16]. Cancer oncogenes are frequently linked to the aberrant expression of BCL-2 family members. These proteins, encompassing antiapoptotic and pro-apoptotic components, govern cell destiny through a complex network of interactions. Antiapoptotic proteins such as BCL-2, BCL-XL, and MCL-1 obstruct apoptotic signals and promote cellular survival [6]. The overexpression of antiapoptotic BCL-2 proteins facilitates the advancement of cancer and confers resistance to therapy.

Apoptosis is an essential mechanism for preserving cellular homeostasis and transpires through two primary pathways: Extrinsic and intrinsic. The BCL-2 protein family in the intrinsic route comprises pro-apoptotic and antiapoptotic members that regulate mitochondrial outer membrane permeability and cytochrome c release, resulting in cell death [17]. In normal cells, BCL-2 suppresses apoptosis by interacting with pro-apoptotic proteins Bax and Bak. Antiapoptotic BCL-2 proteins are often expressed in numerous hematological malignancies, including T-ALL. This overexpression enables cancer cells to circumvent apoptosis and advance tumors, disrupting the apoptotic machinery and facilitating the formation and sustenance of the malignant phenotype. Under typical physiological settings, the equilibrium between pro and antiapoptotic signals regulates cellular turnover. In cancer, this equilibrium is frequently disturbed. The heightened expression of antiapoptotic proteins enables malignant cells to endure therapeutic stress and persist in survival [6].

Research indicates that BCL-2 is significantly expressed in T-ALL cells, particularly in cases exhibiting a more aggressive disease progression [18]. Moreover, BCL-2 has demonstrated interactions with additional oncogenic proteins, including Notch1 and PI3K/AKT, facilitating the survival and proliferation of T-ALL cells [19, 20]. In T-ALL, the disruption of apoptotic pathways is recognized as a significant characteristic. The BCL-2 protein is crucial in treatment resistance and the advancement of illness. Increased concentrations of BCL-2 or other antiapoptotic proteins enable T-ALL cells to circumvent the detrimental effects of chemotherapeutic agents, hence sustaining leukemia viability [21].

Numerous investigations have demonstrated that BCL-2 is significantly expressed in specific cases of T-ALL and correlates with an unfavorable prognosis and an increased likelihood of disease relapse [22]. The upregulation appears to confer a survival advantage to leukemia cells, enabling them to resist pro-apoptotic signals triggered by chemotherapy. BCL-2's significance in T-ALL is underscored by its involvement in treatment resistance mechanisms. Studies indicate that T-ALL cells with elevated BCL-2 expression demonstrate reduced sensitivity to apoptosis triggered by chemotherapeutic agents such as glucocorticoids and anthracyclines. This resistance is partially attributable to BCL-2's capacity to suppress the activation of pro-apoptotic proteins and limit cytochrome c release from mitochondria, interrupting the apoptotic pathway [23].

Current effective therapeutic therapies for tumor cells encompass chemotherapy, targeted therapy, and immunotherapy, with apoptosis representing the most significant form of cell death these agents generate [24]. Dysregulation of Bcl-2 family proteins facilitates oncogenesis. Following the identification of the Bcl-2 family, there has been a transformation in the comprehension of their role in regulating cell survival, especially BCL-2 as an apoptosis regulator, which is intrinsically linked to tumor development, regression, and resistance to cell death [25].

Currently, three categories of inhibitors specifically target the BCL-2 family both intracellularly and extracellularly: Antisense oligonucleotide formulations [26], peptide inhibitors [27], and small molecule inhibitors [28]. Small-molecule inhibitors are the most utilized, with significant scientific importance and promising development potential. BCL-2 inhibitors engage with BCL-2 family members to diminish the synthesis of antiapoptotic proteins, obstruct the tumor cell's antiapoptotic defense, substitute and liberate pro-apoptotic proteins, promote apoptosis, and consequently elicit antitumor effects.

Targeting BCL-2

In recent years, targeting BCL-2 proteins has emerged as a promising therapeutic approach for treating numerous cancer types. Research indicates that BCL-2 and its family members exhibit aberrant expression in various malignancies, including acute leukemias, lymphomas, and solid tumors [29]. In T-ALL, the BCL-2 protein facilitates the evasion of chemotherapy's cytotoxic effects by leukemia cells, with heightened expression notably observed in T-ALL variants unresponsive to conventional therapies [30].

Multiple studies underscore the significance of blocking BCL-2 proteins in managing T-ALL (Table 2). Research utilizing T-ALL animal models has demonstrated that inhibiting BCL-2 significantly diminishes tumor growth and enhances survival rates [31]. These findings underscore the potential significance of targeted therapy approaches against BCL-2 in managing T-ALL. Clinical research indicates that combining chemotherapeutic agents with BCL-2 inhibitors may decrease relapse rates and enhance patient survival. Research has shown that the inhibition of BCL-2, when used alongside conventional chemotherapy agents, substantially enhances treatment results for individuals with acute leukemia [32]. The data demonstrate that targeting BCL-2 can significantly diminish treatment resistance and enhance outcomes in resistant tumors.

Table 2. Studies of using venetoclax alone or combined with other inhibitors

Results Summary	BCL-2 Inhibitor Type	Study
This study provides rational combination strategies involving selective BCL-2 and PI3K/AKT inhibition in B-ALL cell lines.	BCL-2 inhibitor and PI3K/AKT pathway inhibition	Combined BCL-2 and PI3K/AKT pathway inhibition [11]
Their data support the consideration of Venetoclax-based regimens in pediatric patients with R/R ALL/LBL.	Venetoclax, BCL-2 inhibitor	Venetoclax for children and adolescents with acute lymphoblastic leukemia [55]
Study showed promising safety and efficacy in relapsed/refractory T-ALL cases.	Lisaftoclax (APG-2575)	Novel BCL-2 inhibitor lisaftoclax study [92]
Highlighted variability in BCL-2, BCL-2L1, and MCL-1 expression in T-ALL samples, Investigated mechanisms of resistance to Venetoclax.	Venetoclax	Venetoclax-resistant T-ALL [93]
The dual inhibitor of BCL-2/BCL-XL showed effectiveness against T-ALL by also targeting LCK and ACK1 signaling pathways.	NWP-0476	Dual targeting with NWP-0476 [94]
ABT-199 effectively targeted high BCL-2 expression in human T-ALL, suggesting therapeutic potential for relapsed cases.	ABT-199	ABT-199 study [95]
Demonstrate that S55746 is a novel, well-tolerated BH3-mimetic targeting selectively and potently the BCL-2 protein.	BCL-2 selective and potent inhibitor	S55746 study [96]

BCL-2 proteins are also implicated in other malignancies, including non-Hodgkin lymphoma and solid tumors. Research indicates that elevated BCL-2 expression in lymphomas correlates with higher resistance to chemotherapy and radiation [33]. In solid malignancies such as breast and lung cancer, elevated BCL-2 expression facilitates disease development and confers resistance to conventional therapies [34].

Iacovelli et al. (2015) found that concurrently targeting the BCL-2 and mTOR pathways induces synergistic apoptosis in resistant acute lymphoblastic leukemia models, with effective results in ABT-737-resistant samples. The study highlighted the importance of the MCL-1/BCL-2 ratio and the role of MCL-1 modulation, although it did not directly correlate with apoptosis changes [35].

In another study, Chonghaile et al. (2014) found that T-ALL cell lines and patient samples generally rely on BCL-XL for survival, except in ETP-ALL cases where BCL-2 is crucial. This dependency influences sensitivity to BH3 mimetics ABT-263 and ABT-199, highlighting BCL-2 as a potential therapeutic target in ETP-ALL [36]. Also, Tzifi et al. (2012) examined BCL-2 family proteins in leukemias, emphasizing their role in apoptosis regulation and potential links to cancer pathophysiology and chemotherapy resistance, with ongoing research aimed at understanding these proteins' prognostic impacts to develop new therapies for improved patient survival [37].

The targeting of BCL-2 proteins as a potential therapeutic approach in malignancies, especially T-ALL, has garnered significant interest. Laboratory and clinical research demonstrate that BCL-2 inhibition may mitigate drug resistance and enhance therapeutic results in several malignancies. Nonetheless, additional research and development are essential to establish more efficacious treatment techniques with reduced side effects for individuals with various cancer types.

Considering the function of BCL-2 in treatment resistance, inhibiting this protein has become a promising therapeutic approach for T-cell T-ALL. BCL-2 inhibitors are engineered to counteract the antiapoptotic properties of BCL-2 and reinstate the susceptibility of leukemic cells to standard treatments. Venetoclax (ABT-199), a thoroughly researched BCL-2 inhibitor, preferentially interacts with BCL-2 and promotes apoptosis in malignancies reliant on BCL-2. Venetoclax has demonstrated efficacy in multiple hematologic malignancies, notably CLL and AML, especially in instances characterized by elevated BCL-2 expression [29]. The use of venetoclax for T-ALL is presently under rigorous evaluation. Initial findings indicate that combining venetoclax with conventional chemotherapeutic agents may augment therapeutic efficacy and surmount drug resistance [38].

Venetoclax, a novel anticancer agent with a targeted mechanism of action, is utilized in managing many hematologic malignancies. This medication has shown to be very efficacious for CLL and certain lymphomas, signifying a significant advancement in managing these conditions. Abbott Laboratories initially investigated the medication in partnership with Genentech to treat hematologic malignancies. In April 2006, it received approval in the United States for administration to patients with CLL, those with deletions on chromosome 17 (17 Del), and individuals who had previously undergone treat-

ment. The medication exhibits a strong affinity for BCL-2 and can bind to BCL-XL and BCL-W. Venetoclax binds to BCL-2, displacing proteins such as Bim, which results in enhanced membrane permeability, activation of the apoptosis cascade, and, finally, the apoptosis of cancer cells [39]. Venetoclax, a potent and selective inhibitor of the BCL-2 protein, has demonstrated therapeutic effectiveness in various hematological malignancies.

In contrast to navitoclax, which inhibits BCL-2 and BCL-XL, venetoclax selectively binds to BCL-2 with sub-nanomolar affinity, effectively neutralizing it while exhibiting minimal interaction with BCL-XL. By preserving BCL-XL, venetoclax exerts a negligible effect on platelet numbers. In preclinical investigations, this bioavailable oral inhibitor has shown cytotoxic action against multiple cell lines, including those originating from ALL, non-Hodgkin's lymphoma, and AML cell types. In xenograft models of hematological cancers, venetoclax demonstrated tumor growth suppression in a dose-dependent manner. In animals where venetoclax had poor efficiency as a monotherapy, its effectiveness was enhanced when administered in conjunction with other pharmacological agents [40-42].

A comprehensive clinical trial demonstrated that venetoclax, as monotherapy or in conjunction with other agents, significantly diminished tumor burden, enhancing patient outcomes [43]. In patients with treatment-resistant lymphomas, venetoclax, particularly in conjunction with other therapies such as chemotherapy or monoclonal antibodies, has shown a beneficial effect on disease management [44]. A recent study demonstrated that venetoclax may selectively affect treatment-resistant lymphomas and could be a viable choice for patients who do not respond to conventional therapy [45]. Venetoclax is being investigated as a possible treatment option for AML, particularly in conjunction with chemotherapy. Preliminary findings indicated that venetoclax could enhance treatment response and serve as a crucial therapeutic alternative for individuals with AML [46].

The association between BCL-2 protein overexpression and cancer is established. BCL-2 expression is a crucial survival factor promoting carcinogenesis and treatment resistance by preventing cancer cells from apoptosis. Lymphoid cancers frequently demonstrate BCL-2 overexpression, rendering BCL-2 inhibitors an attractive treatment alternative [47-49].

Venetoclax is a pioneering oral and accessible BH-3 mimic developed by reverse design to bind BCL-2, exhibiting significantly lower affinity for BCL-W and BCL-XL, which is essential for platelet survival. Venetoclax exhibits a strong affinity for BCL-2, interfering with cellular communication and triggering a TP53-independent apoptotic mechanism. This treatment paradigm has revolutionized CLL therapy and is particularly interested in other hematological malignancies, including non-Hodgkin's lymphoma, multiple myeloma, and AML [50-52].

The cytotoxicity of venetoclax in lymphoid cells is largely contingent upon the activation of BAX and BAK, owing to its action method. Research with the pan-caspase inhibitor Z-VAD demonstrated that venetoclax-induced cell death is contingent upon caspase activation. Moreover, Bim seems to be the principal catalyst of apoptosis triggered by this BH3 mimic, as the cellular susceptibility to venetoclax was significantly diminished in Bim-deficient cells. Nonetheless, differing degrees of resistance attributed to the lack of BIM were noted in various lymphocyte subsets [53].

The efficacy of venetoclax in pediatric ALL was investigated owing to its superior tolerability and the sensitivity of ALL xenografts to BCL-2 inhibition by navitoclax. A significant association was seen between inadequate response to venetoclax and BCL-XL expression. In contrast to CLL cells, which primarily rely on BCL-2 expression, most ALL xenografts necessitated concurrent suppression of both BCL-2 and BCL-XL, elucidating the varying results observed with venetoclax and navitoclax. Xenografts from child acute lymphoblastic leukemia with mixed leukemia were the exception, as venetoclax demonstrated effects comparable to navitoclax, indicating a potentially intriguing category for clinical trials with venetoclax [54].

Gibson et al. (2022) found that venetoclax, a treatment for acute lymphoblastic leukemia and lymphoblastic lymphoma, was effective in 18 patients aged 22 years. No deaths occurred within 30 days of treatment initiation, and complete remission was achieved in 11 patients (61%). However, three patients reached complete response (CR) and later relapsed and died, and 9 died. The study supports using venetoclax-based regimens in pediatric R/R ALL/LBL patients [55]. Also, Lew et al. (2022) study on venetoclax and pro-apoptotic targeting in lymphoid malignancies showed its effectiveness against various B-cell non-Hodgkin's lymphomas, acute lymphoblastic leukemia and multiple myeloma. Combining venetoclax with standard regimens showed promise, but further research is needed to optimize dosage and timing [56].

In addition, Tahir et al. studied venetoclax resistance in seven cell lines, finding increased expression of antiapoptotic proteins BCL-XL and MCL-1, reduced expression of pro-apoptotic proteins, and mutations in the BH3 binding groove, which could interfere with venetoclax binding [57].

In addition to the primary applications noted, venetoclax is under ongoing investigation for the treatment of several hematological malignancies and certain solid tumors. Current investigations into novel applications of venetoclax encompass clinical studies for breast, prostate, and lung cancers. These investigations may facilitate novel applications of venetoclax and enhance therapy results across diverse cancer types [58].

Through ongoing investigations and clinical testing, this medicine may substantially improve therapeutic outcomes and diminish side effects in individuals with hematologic malignancies. Continued research and novel inquiries may enhance clinical applications and foster the creation of new therapeutic procedures employing venetoclax.

Combination Therapy With Venetoclax and Other Treatments

Venetoclax is utilized not only as a monotherapy but also in conjunction with various classes of agents, including DNA-damaging chemotherapeutics, anti-CD20 antibodies (rituximab and obinutuzumab) [59], proteasome inhibitors (bortezomib and carfilzomib) [60], hypomethylating agents (azacitidine or decitabine) [61], kinase inhibitors (sunitinib, ibrutinib, idelalisib, dinaciclib, cobimetinib) [62], MDM2 inhibitors (idasanutlin) [63], and inhibitors of antiapoptotic molecules such as BCL-XL and Mcl-1 [64]. The justification for these combinations is that, unlike CLL, follicular lymphoma (FL), mantle cell lymphoma (MCL), and Waldenström macroglobulinemia—which are marked by elevated levels of BCL-2 and a substantial dependence of malignant cells on this molecule for survival and resistance—other hematological malignancies (such as diffuse large B-cell lymphoma, ALL, multiple myeloma, AML, and CML) display a more heterogeneous expression pattern of this antiapoptotic molecule. Its role in cellular resistance to apoptosis is not universal [65]. Resistance to venetoclax has been documented to correlate with the overexpression of BCL-XL and/or MCL-1. In some instances, simply decreasing BCL-2 cannot attain significant clinical outcomes [66]. As a result, multiple combinations are being investigated in different clinical environments, with venetoclax being combined with agents chosen according to the molecular pathways disrupted in certain cancers.

Seyfried et al. (2022) studied the effects of venetoclax, S63845, and A-1331852 on pre-B ALL cell lines and patient-derived cells. Results showed heterogeneous sensitivity to these inhibitors, with some venetoclax-resistant leukemias sensitive to selective antagonists of MCL-1 or BCL-XL. Venetoclax-treated ALL cells rely on MCL-1 and BCL-XL, suggesting MCL-1 or BCL-XL are vulnerabilities in BCL-2-inhibited cells. In vivo, the combined effects of venetoclax and S63845 showed enhanced antileukemic activity in a patient-derived xenograft preclinical model [64].

Liu et al. (2022) evaluated the effectiveness of combined ibrutinib and venetoclax for first-line treatment of CLL. The study involved 80 patients who were previously untreated. Results showed that 56% of patients achieved undetectable residual disease in the bone marrow after 12 cycles and 66% at 24 cycles. Overall, 75% of patients achieved the best response, with 93% achieving a three-year progression-free survival [66].

Li et al. (2023) investigated the effects of MCL-1 inhibitors and venetoclax on T-ALL cell lines. They identified two resistant cell lines but found no correlation between MCL-2 and BCL-2 levels and drug resistance. The study also found a significant reduction in cell viability in cells treated with both inhibitors compared to those treated with only one [67].

Challenges of Venetoclax Therapy and Improvement Strategies

The administration of venetoclax encounters obstacles that require continuous investigation and progress. The formation of drug resistance is a serious challenge in the usage of venetoclax. Resistance to venetoclax may develop due to genetic modifications in cancer cells or by reconfiguring apoptotic signaling pathways [68]. Alterations in the expression of BCL-2 family members, including BCL-XL and MCL-1, may result in resistance to venetoclax. Recent studies indicate that cancer cells can acquire resistance by enhancing the synthesis of these proteins or by activating alternate apoptotic pathways [69].

One of the principal challenges is the up-regulation of alternative antiapoptotic proteins (intrinsic and acquired resistance). Venetoclax induces apoptosis in cancer cells by inhibiting the antiapoptotic protein BCL-2. However, cancer cells can develop resistance through the up-regulation of other antiapoptotic proteins, such as MCL-1 and BCL-XL. These proteins can compensate for the inhibited BCL-2, thereby safeguarding cancer cells from

apoptosis even in the presence of Venetoclax. To address this resistance, research investigates the combination of venetoclax with MCL-1 or BCL-XL inhibitors. Such combinations may enhance treatment effectiveness by mitigating the alterations in BCL-2, and impaired drug binding is regarded as a significant hurdle in the treatment of venetoclax. Venetoclax must interact with the active site of the BCL-2 protein to trigger apoptosis. In certain instances, genetic mutations in BCL-2 induce structural alterations that hinder the efficient binding of venetoclax. This leads to diminished medication efficacy. These mutations represent acquired resistance mechanisms and are commonly detected in patients following extended treatment durations [70, 71]. The development of medications that target alternative locations on BCL-2 or distinctly interact with this protein may mitigate this kind of resistance.

The activation of alternative survival pathways presents an additional challenge. Cancer cells can evade apoptosis triggered by venetoclax by engaging other survival mechanisms. Signaling pathways such as PI3K/AKT and NF-κB, which facilitate cancer cell survival and proliferation, may become increasingly active and mitigate the effects of BCL-2 suppression. These alternative pathways serve as supplementary strategies for counteracting the effects of venetoclax [10, 72]. Combining venetoclax with inhibitors that target pathways like PI3K or NF-κB is being investigated as a therapeutic strategy to improve treatment outcomes.

Another problem is the tumor microenvironment and cellular interactions; specifically, cancer cells engage with other cells within the tumor microenvironment, including immune and supporting cells. These interactions may generate survival signals for cancer cells, enabling them to withstand venetoclax therapy. For instance, stromal cells within the bone marrow can release cytokines and growth factors that facilitate the evasion of death by leukemia cells [73]. Targeting the tumor microenvironment and inhibiting these cellular interactions is a possible strategy to address this issue. Pharmaceuticals that interfere with these interactions are being studied as possible supplements to venetoclax treatment.

A further difficulty is the emergence of resistance resulting from alterations in the therapeutic dosing regimen or temporary cessation of treatment. Patients may need to decrease their dosage or suspend treatment due to adverse effects, allowing cancer cells the chance to build resistance. This phenomenon is especially seen in individuals with CLL [74, 75]. Vigilant surveillance of pharmacological levels and modification of treatment regimens according to patient response is essential for optimal management of this concern.

The resistance mechanisms present considerable obstacles to the application of venetoclax, underscoring the necessity for combination therapies and innovative techniques to improve its effectiveness. Current research seeks to enhance treatment efficacy and mitigate resistance to venetoclax.

Adverse effects linked to venetoclax are a significant obstacle in therapy. Frequent adverse consequences encompass infections resulting from diminished white blood cell counts, hematological illnesses such as anemia, and gastrointestinal complications. Moreover, the incidence of tumor lysis syndrome (TLS), especially at elevated dosages and in individuals with significant tumor burden, might result in severe consequences necessitating vigilant monitoring and suitable management [76]. Combination therapy with venetoclax is presently under investigation as a viable approach for specific malignancies. The coordination and accurate dosing of various combinations provide a considerable barrier. The concomitant use of venetoclax with other pharmacological agents, such as chemotherapy or monoclonal antibodies, may result in drug interactions and heightened adverse effects. Establishing the optimal dosage and addressing side effects in these combination medicines necessitates a comprehensive investigation [77].

Recent studies have concentrated on enhancing the effectiveness and minimizing the adverse effects of venetoclax. A notable advancement is the formulation of combination treatment strategies using venetoclax with additional pharmaceuticals. Clinical investigations have shown that the combination of venetoclax with other anticancer drugs can enhance treatment efficacy and diminish the occurrence of side effects [78]. Research increasingly focuses on identifying and targeting novel molecular mechanisms to overcome medication resistance. The integration of venetoclax with medicines targeting alternative BCL-2 family proteins, namely BCL-XL and MCL-1, has surfaced as a novel approach. Moreover, developing biomarkers that predict response to venetoclax therapy may facilitate the personalization of treatment and enhance therapeutic outcomes [79]. Improvements in the surveillance and management of adverse effects are also essential. The establishment of exact guidelines for the prevention and management of TLS and associated adverse effects, particularly in patients with significant tumor loads, has enhanced therapeutic outcomes [80].

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Venetoclax Safety Profile

Venetoclax possesses a safety profile that underscores many possible concerns. The focused action on the BCL-2 protein offers therapeutic benefits while also raising safety concerns. TLS arises when tumor cells are swiftly eradicated, releasing their intracellular constituents into the bloodstream [81]. Patients may exhibit hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, accompanied by symptoms such as nausea, vomiting, muscle cramps, seizures, and arrhythmias. Risk classification is essential to avert TLS, and patients identified as high-risk may necessitate pre-treatment hydration and electrolyte surveillance [82]. Hematologic toxicities encompass neutropenia, thrombocytopenia, anemia, and gastrointestinal adverse effects such as nausea, vomiting, diarrhea, and constipation. Supportive care utilizing antiemetics or antidiarrheals is generally implemented to mitigate these side effects [83]. Prolonged use of venetoclax poses long-term hazards, including the potential development of secondary malignancies, as BCL-2 inhibition may increase the likelihood of new cancer formation in patients [84]. The cardiovascular effects indicate a risk of arrhythmias in patients administered venetoclax, particularly in individuals with pre-existing cardiac problems. Consistent cardiac monitoring is recommended, particularly for high-risk patients [85].

Comparative Safety With Other Therapies

Venetoclax's safety profile is contrasted with conventional chemotherapy, which frequently induces myelosuppression, resulting in neutropenia, thrombocytopenia, and anemia. These therapies elevate the risk of infections and necessitate rigorous care. Chemotherapy induces significant gastrointestinal damage, necessitating antiemetic treatments and nutritional assistance. Chimeric antigen receptor T-cell treatment is associated with cytokine release syndrome, which may induce significant systemic inflammatory reactions and prolonged consequences [86]. Neurotoxic consequences, including disorientation, seizures, and encephalopathy, may result in enduring difficulties. Hematological consequences may manifest, with certain individuals enduring extended cytopenias. Monoclonal antibodies, such as blinatumomab, are associated with immune-related adverse effects, albeit of lesser severity [87-96]. Myelosuppression is lower than with conventional chemotherapy but still significant, and regular monitoring is essential to manage any hematological toxicities.

Conclusion

T-ALL is a challenging type of leukemia with abnormal and aggressive T-cell proliferation and resistance to conventional treatments. Venetoclax, a novel therapeutic option targeting the BCL-2 protein, has shown potential in treating T-ALL by decreasing cancer cell survival. By inducing programmed cell death in cancer cells, venetoclax can reduce tumor burden and improve clinical outcomes. However, venetoclax faces challenges like drug resistance from alterations in other BCL-2 family proteins or alternative apoptotic pathways. Side effects also pose challenges, especially in patients with high tumor burdens and high doses. Low white blood cell counts and other hematological disorders may require supportive and preventive measures.

Venetoclax, when used in combination with other treatments, can improve treatment responses and extend survival in patients with T-ALL. However, it faces challenges like drug resistance, which may arise from BCL-2 protein modifications or alternative apoptotic pathways. Further research is needed to understand resistance mechanisms and develop new therapeutic options. Adverse effects, such as TLS, necessitate strict monitoring and management. Supportive and preventive interventions may also be needed.

Recent breakthroughs in clinical and laboratory research illustrate the significant potential of venetoclax in treating T-ALL and other hematological malignancies. Current investigations aim to improve the effectiveness and reduce the adverse effects of this medication. Venetoclax, when utilized alongside chemotherapy and monoclonal antibodies, has demonstrated encouraging outcomes, especially in combination regimens.

In summary, venetoclax, a targeted medication, has significantly progressed in treating hematological malignancies, particularly T-ALL. However, issues like drug resistance and adverse effects persist. Advancements in understanding resistance mechanisms, refining treatment strategies, and mitigating side effects suggest a promising future for venetoclax, with ongoing research promising improved outcomes and reduced side effects.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors contribution's

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interest.

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