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Preclinical and Case Series Studies on the Combination of Venetoclax with Epigenetic Drugs in T-Cell Acute Lymphoblastic Leukemia

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Abstract: Adult T-cell acute lymphoblastic leukemia (T-ALL) exhibits a dismal prognosis characterized by low remission rates, high relapse rates, and poor tolerance to conventional chemotherapy. The urgent development of novel therapeutic strategies is imperative to improve clinical outcomes. In this study, we propose a dual epigenetic targeting regimen combining Venetoclax with Chidamide and Azacitidine. Preclinical investigations demonstrated synergistic anti-proliferative effects of this triple-drug combination against Jurkat cells in vitro. Additionally, we retrospectively analyzed clinical data from five high-risk T-ALL patients to evaluate the regimen's efficacy and safety. Among the cohort (all male; median age 55 years, range 25–72), one patient had refractory T-ALL (R-TALL) following VDCP regimen induction failure, while four were newly diagnosed (ND-TALL). After one treatment cycle, four patients achieved complete remission (CR) or CR with incomplete hematologic recovery (CRi), with one additional patient attaining CR after the second cycle. Four patients achieved deep molecular remission (MRD-negative status) within two cycles, while two successfully underwent allogeneic hematopoietic stem cell transplantation (HSCT) during sustained remission. Myelosuppression emerged as the predominant treatment-related adverse event. These preclinical and clinical findings collectively support the therapeutic potential of the Combination of Venetoclax with Epigenetic Drugs as a promising option for high-risk T-ALL patients.

Keywords: acute T-lymphoblastic leukemia, epigenetics, chidamide, venetoclax, efficacy, safety

Introduction

Acute lymphoblastic leukemia (ALL), a hematologic malignancy with an incidence of 17.3 per million, manifests as T-cell lineage (T-ALL) in approximately 25% of adult cases.[1] The pathogenesis of T-ALL involves malignant transformation and clonal expansion of T-cell precursors in the bone marrow and thymus, manifesting as anemia, bleeding diathesis, heightened infection susceptibility, and tissue infiltration.[2] Adult patients with T-ALL face poor outcomes, characterized by a relapse rate of approximately 50% within 1 year of remission and a 5-year overall survival of around 40%. The dismal prognosis of adult T-ALL drives urgent exploration of effective therapies. Building on their success in hematologic cancers, targeted therapies present promising options for T-ALL. Numerous research centers are currently conducting clinical trials that combine targeted therapies with traditional chemotherapy, aligning with the prioritization and recommendation of international T-ALL treatment guidelines.[3] T-ALL demonstrates greater aggressiveness and a poorer prognosis compared to other leukemias, likely due to the unique developmental and differentiation mechanisms of T-lymphocytes. Unlike other immune cells, T-cells undergo complex maturation processes dependent on intricate signaling pathways within the thymic microenvironment. Epigenetic regulation plays a critical role in this process: during normal T-cell differentiation, the transition from double-negative (DN) to double-positive (DP) and ultimately to single-positive (SP) CD4+ T-cells is driven by DNA demethylation, whereas histone acetylation dynamically regulates CD8+ T-cell gene expression.[4] Given the central role of epigenetics in T-cell development, it is unsurprising that T-ALL is

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strongly linked to epigenetic dysregulation. Indeed, over 80% of T-ALL-related gene mutations affect epigenetic modifiers,[5,6] highlighting their pivotal contribution to leukemogenesis. T-ALL is closely related to epigenetic variations, with over 80% of T-ALL-related gene mutations affecting epigenetic modifications. Consequently, a deeper understanding of these epigenetic mechanisms may uncover novel therapeutic targets and improve treatment strategies for T-ALL. Venetoclax, a highly selective BCL-2 inhibitor, has revolutionized the therapeutic paradigm for acute myeloid leukemia (AML) and significantly transformed treatment strategies for myeloid malignancies. The BCL-2 protein, as its primary molecular target, serves as a crucial anti-apoptotic regulator that plays a pivotal role in the pathogenesis of various hematological malignancies. Notably, early T-cell precursor acute lymphoblastic leukemia (ETP-ALL) demonstrates marked sensitivity to venetoclax treatment due to its characteristic overexpression of BCL-2 protein. This distinctive pharmacological response not only highlights the therapeutic potential of venetoclax in T-ALL but also identifies a novel actionable target for precision therapy in this disease.[7] In this study, we propose a novel targeted therapeutic regimen combining venetoclax with dual epigenetic-modulating agents (Chidamide and Azacitidine) for the treatment of T-ALL. In vitro studies have confirmed the synergistic anti-T-ALL effect of this triple-drug combination. Preliminary clinical observations in five treated patients further support its promising efficacy and manageable safety profile.

Basic Research

Previous studies have demonstrated that the combination of chidamide, venetoclax, and azacitidine exerts a synergistic inhibitory effect on Jurkat cells (human T lymphoblastic leukemia cells).[8] In vitro experimental investigations have revealed that Azacitidine, Chidamide, and Venetoclax individually exhibit proliferative inhibitory effects on Jurkat cells, with the order of intensity being CS055 (Chidamide) > Vene (Venetoclax) > Azac (Azacitidine). When used in pairwise combinations or as a three-drug combination, the cytotoxic effects on leukemia cells are concentration-dependent. Notably, even at lower doses, significant drug synergy is observed in both Azac + Vene and CS055 + Vene combinations. Initially, an antagonistic effect was observed for the combination of Azac and CS055 at low doses, however, when the doses of both drugs reached 1.25μM+1μM, their combined CI value was less than 1 indicating a synergistic effect. Furthermore, at doses of 2.5μM for Azac and 2μM for CS055 respectively, the CI value between these two drugs decreased to 0.0004 demonstrating stronger synergy compared to the Azac + Vene (CI=0.0032) and CS055 + Vene (CI=0.0034) combinations at equivalent concentrations levels. Finally, a synergistic proliferative inhibitory effect on Jurkat cells was consistently observed across all gradient concentration levels following treatment with Azac + Vene + CS055.

Case Series Report

Materials and Methods

A retrospective analysis was conducted on the efficacy of venetoclax combined with chidamide and azacitidine in 5 patients with T-ALL treated at the Hematology Department of Sichuan Provincial People's Hospital between April 2023 and May 2024. All clinical cases included in this study were approved by the Ethics Committee of Sichuan Provincial People's Hospital (Approval No. 2024–230), and written informed consent forms were obtained from all patients. Patient samples and research data were obtained by retrieving the medical record system of Sichuan Provincial People's Hospital. Patient information collected included gender, age, initial diagnostic laboratory parameters (results of blood cell tests, bone marrow morphology examinations, flow cytometry analysis, molecular biology assays, and cytogenetic tests), as well as treatment-related data (therapeutic regimens, efficacy evaluation results, adverse reactions, and transplantation timing). The specific treatment regimens for the five patients were as follows: Chidamide 30mg twice a week, orally; Azacitidine 75mg/m2, d1-d7, subcutaneous injection; venetoclax 100mg d1, 200mg d2, 400mg d3-d14, orally; dexamethasone 10mg, d1-d7/d1-d10, intravenous injection/oral administration (specific dosages adjusted based on the patient's condition). Each cycle lasted 28 days, with efficacy assessment conducted after each cycle. (Clinical baseline characteristics of the 5 patients is shown in Table 1, course of treatment is shown in Figure 1).

Table 1 Clinical Baseline Characteristics of Patients

Clinical Features	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	25	55	58	26	72
Gender	Male	Male	Male	Male	Male
Type	R T-ALL	ND T-ALL	ND T-ALL	ND T-ALL	ND T-ALL
Mediastinal mass	No	No	No	Yes	No
Lymphnodes	No	Yes	Yes	Yes	No
CNS involvement	No	No	No	No	No
WBC (x109/L)	113.4	212.9	2.7	0.6	100.0
Hb (g/L)	65	119	144	50	89
PLT (x109/L)	34	39	211	19	66
PB blast (%)	85.0	91.9	0	28.2	90.9
BM blast (%)	83.0	85.0	20.5	70.0	90.0
Abnormal blast in FCM (%)	90.0	91.6	22.7	30.6	95.4
Surface antigen	cCD3+CD7+CD5+CD34 +CD33dim	CD7+CD5+CD1dimCD2dimCD3dimCD34dim	CD7+cCD3dimCD2dimCD5dimCD34dim	cCD3+CD7+CD2dim	cCD3 +CD38 +CD34 +CD7cTDT +CD5dim
Subtype	Pro-T	Pre-T	ETP-ALL	MPAL (T/My)	Pro-T
Karyotype	46,XY, del(5)(q31)t(10;11)(p13;q23)	46,XY	46,XY	46,XY	Unchecked
Genetics	NRAS; NOTCH1;WT;KIT; MYB; TET1; DNM2	BCOR; IDH2; NRAS; NOTCH1; DNMT3A; FAT1; ERCC5; BCOR	Unchecked	PHF6; FAT3; SETD2; HOXA10; TP53; EED; USH2A; BRCA2; FANCN; JARID2; NCOR1; SF3B1	Unchecked

Case Reports

Patient 1: A 25-year-old Tibetan male was admitted with abnormal blood tests: white blood cell count 113.41 × 10^9/L, hemoglobin 65 g/L, platelet count 34 × 10^9/L, and peripheral blood blasts + immature cells at 85%. Bone marrow puncture confirmed a diagnosis of Pro-T-ALL, with primitive+immature lymphocytes comprising approximately 83%. Additional testing revealed the CALM-AF10 fusion gene, a karyotype of del(5)(q31), t(10;11)(p13;q23), and mutations in NRAS, NOTCH1, WT1, KIT, MYB, and TET1 genes. The patient received initial induction therapy with the VID regimen. Following one cycle, no remission was achieved, with measurable residual disease (MRD) at approximately

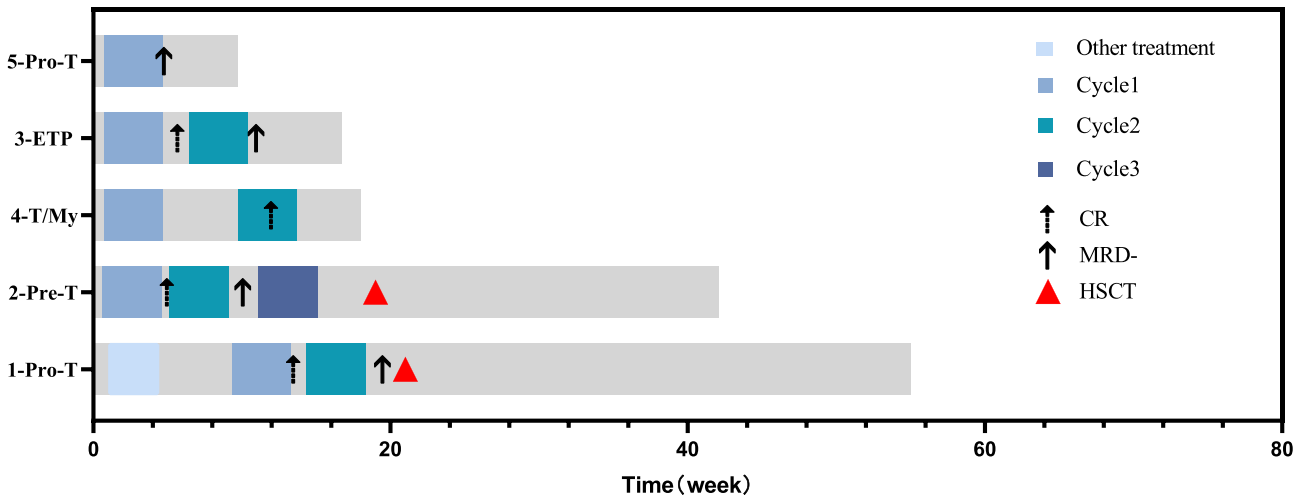

Figure 1 Five Patients' course of treatment. This timeline diagram illustrates the treatment trajectories and key clinical events of five patients (with the y-axis displaying immunophenotypic profiles: Pro-T, ETP, T/My, Pre-T, Pro-T) over an 80-week period. The x-axis represents time (weeks), where color-coded blocks correspond to distinct treatment cycles.

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90%. Subsequently, the Venetoclax plus Chidamide and Azacitidine regimen was initiated. This treatment resulted in severe grade 4 neutropenia and grade 4 thrombocytopenia (CTCAE v5.0), complicated by a grade 3 pulmonary infection. Management included granulocyte colony-stimulating factor, blood transfusion, and antibiotics, leading to symptom improvement and achievement of CRi after one cycle. During the second cycle, gradual hematologic recovery occurred without recurrent hematologic adverse events or pulmonary infections. Attainment of MRD negativity was followed by allogeneic hematopoietic stem cell transplantation (allo-HSCT), resulting in sustained remission.

Patient 2: The patient is a 55-year-old male who was admitted with leukocytosis. The routine blood test revealed the following results: white blood cell count of 212.9 x 10^9/L, hemoglobin level of 119g/L, platelet count of 39 x 10^9/L, peripheral blood blast + immature cell rate of 91.9%, accompanied by cervical lymphadenopathy. Following a bone marrow puncture, the diagnosis was confirmed as Pre-T-ALL without abnormalities in fusion genes or chromosomal karyotype; however, gene monitoring showed abnormalities in BCOR, IDH2, NOTCH1, NRAS, DNMT3A, FAT1, ERCC5 and BCOR genes. After receiving induction therapy with Venetoclax plus Chidamide Azacitidine dual epigenetic target regimen upon definitive diagnosis achievement; during the first cycle of induction treatment adverse reactions were observed including severe neutropenia and thrombocytopenia (CTCAE grade 4), as well as severe anemia (CTCAE grade 3) due to bone marrow suppression. Symptomatic treatment involving blood cell transfusion, platelet transfusion and granulocyte colony-stimulating factor administration effectively improved the condition. Additionally, the patient experienced pulmonary infection (grade 3) and abdominal infection (grade 3), which were successfully treated using meropenem, linezolid, tigecycline, and amphotericin B.Subsequent treatment cycles did not result in bone marrow suppression or other adverse events. The patient achieved complete remission with CRi after one cycle of treatment followed by MRD negativity after two cycles. Further consolidation therapy consisting one additional cycle using original regimen was administered prior to hematopoietic stem cell transplantation. Currently, the patient remains in sustained remission.

Patient 2: A 55-year-old male presented with leukocytosis. Admission complete blood count showed: white blood cell count 212.9 $\times$ 10^9/L, hemoglobin 119 g/L, platelet count 39 $\times$ 10^9/L, and peripheral blood blasts+immature cells at 91.9%, accompanied by cervical lymphadenopathy. Bone marrow puncture confirmed Pre-T-ALL. While fusion genes and karyotype were normal, genetic testing revealed mutations in BCOR, IDH2, NOTCH1, NRAS, DNMT3A, FAT1, ERCC5, and BCOR. Following diagnosis, the patient received induction therapy with the Venetoclax plus Chidamide and Azacitidine regimen. During the first cycle, treatment-related adverse events included severe neutropenia and thrombocytopenia (CTCAE v5.0 grade 4), and severe anemia (grade 3) due to bone marrow suppression. Supportive care with red blood cell transfusions, platelet transfusions, and granulocyte colony-stimulating factor effectively managed these cytopenias. Additionally, the patient developed grade 3 pulmonary and abdominal infections, successfully treated with meropenem, linezolid, tigecycline, and amphotericin B. Subsequent treatment cycles were well-tolerated without significant bone marrow suppression or other adverse events. The patient achieved CRi after one cycle and MRD negativity after two cycles. One additional cycle of consolidation therapy with the original regimen was administered prior to proceeding to allo-HSCT. The patient remains in sustained remission.

Patient 3: A 58-year-old male presented with axillary lymphadenopathy. Admission laboratory findings included leukopenia (white blood cell count 2.7 $\times$ 10^9/L). Bone marrow puncture confirmed a diagnosis of ETP-ALL, with blasts and immature lymphocytes comprising 20.5% of the marrow cellularity. Fusion gene testing and chromosomal analysis showed no abnormalities; genetic monitoring was not performed due to financial constraints. The patient received the Venetoclax plus Chidamide and Azacitidine regimen. CR was achieved after one cycle, followed by MRD negativity after two cycles. Treatment was well-tolerated, with only grade 1 elevation of liver enzymes (CTCAE v5.0) observed across both cycles. No hematologic or other adverse events occurred. The patient currently awaits allo-HSCT.

Patient 4: A 26-year-old male presented with pancytopenia: white blood cell count 0.6 $\times$ 10^9/L, hemoglobin 50 g/L, platelet count 19 $\times$ 10^9/L, and peripheral blood blasts + immature cells at 28.2%. CT imaging revealed an anterior mediastinal mass with multiple enlarged axillary and supraclavicular lymph nodes. Bone marrow puncture confirmed mixed-phenotype acute leukemia with T-lymphoblastic and myeloid features (T/My-AML), characterized by 20.5% primitive + immature lymphocytes and 49.5% primitive + early myeloid cells. Fusion gene analysis identified PHF6+, while genetic testing detected mutations in PHF6, FAT3, HOXA10, SETD2, TP53, USH2A, BRCA2, EED, FANCN, JARID2, NCOR1, and SF3B1. The patient received induction therapy with the Venetoclax plus Chidamide and

Azacitidine regimen. After one cycle, primitive myeloid cells decreased to 6% and primitive lymphocytes to 3.5%, achieving partial remission (PR). Due to the persistent mediastinal mass, the Hyper-CVAD-B regimen was added during the second induction cycle: methotrexate (5 g on day 1) and cytarabine (3 g on day 2). This resulted in CRi and a slight reduction in the extramedullary mass. The patient remains MRD positive and is scheduled for consolidation chemotherapy followed by HSCT. The initial induction cycle was complicated by severe hematologic toxicity: grade 3 anemia, and grade 4 thrombocytopenia and neutropenia (CTCAE v5.0). A concurrent grade 3 pulmonary infection developed. Supportive management including blood transfusions and antimicrobial therapy (vancomycin, imipenem-cilastatin, amphotericin B lipid complex) improved symptoms; however, blood counts did not recover.

Patient 5: A 72-year-old male presented with fatigue. Admission complete blood count showed leukocytosis: WBC 100 × 10^9/L, Hb 89 g/L, ANC 3 × 10^9/L, Plt 66 × 10^9/L, with peripheral blood blasts and immature cells comprising 90.9% of leukocytes. Bone marrow puncture confirmed Pro-T-ALL. Genetic and chromosomal analysis was not performed due to financial constraints. The patient received induction therapy with the Venetoclax plus Chidamide and Azacitidine regimen. During treatment, severe grade 4 neutropenia (CTCAE v5.0) and low-grade fever occurred, prompting prophylactic fluconazole administration. After one cycle, the patient achieved CRi and MRD negativity. Within two weeks of induction initiation, severe hematologic adverse events developed: grade 3 anemia, and grade 4 thrombocytopenia and neutropenia (CTCAE v5.0), without evidence of organ dysfunction or severe infection. Hematologic recovery commenced during the third week, with neutrophil and platelet counts normalizing by the end of the first induction cycle. The patient currently remains in continuous remission and is planned for consolidation therapy with the same regimen.

Results

The combination of Venetoclax with Epigenetic Drugs regimen demonstrated significant clinical activity. All five patients (100%) achieved an objective response, with four (80%) attaining CR or CRi within one cycle. Patient 4 (T/My-AML) achieved only PR after the first cycle. MRD negativity was achieved within two cycles by four patients (60%; Patients 1, 2, 3, and 5). Patient 5 achieved both CR and MRD negativity after one cycles, while Patient 4 remained MRD positive. Following treatment, two patients underwent successful allo-HSCT with sustained remission; Patient 3 awaits transplantation (summarized in Table 2).

Treatment-related adverse events were primarily hematologic and manageable with supportive care (summarized in Table 3). All patients (100%) experienced grade 3/4 hematologic adverse events. Grade 4 neutropenia and thrombocy-

Table 2 Summary of Treatment Response

Patient NO.	Cycle 1 Response	Cycle 1 MRD	Cycle to CR/Cri	Cycle to MRD(-)	Prognosis
1	CRi	1.00	1	2	HSCT
2	CRi	0.28	1	2	HSCT
3	CR	0.01	1	2	MRD(-)
4	PR	1.18	2	/	CRi
5	CRi	0	1	/	CRi

Notes: MRD is a monitoring method for detecting tiny residual lesions based on flow cytometry, with a detection limit of 10^-4.

Table 3 Summary of Adverse Events

Adverse Event	Grade 1 (n=5)	Grade 2 (n=5)	Grade 3 (n=5)	Grade 4 (n=5)
Anemia	0	0	**3**	0
Neutropenia	0	0	0	**4**
Thrombocytopenia	0	0	0	**4**
Pneumonia	0	0	**3**	0
Hepatic insufficiency	**2**	0	0	0
Renal insufficiency	**1**	0	0	0
Pruritus	**1**	0	0	0
Nausea	**1**	**2**	0	0

topenia were common, observed in 4 patients (80%). Grade 3/4 anemia occurred in 3 patients (60%). Furthermore, infectious complications were frequent. Grade 3 pulmonary infections occurred in 3 patients (60%; Patients 1, 2, and 4). Patient 2 also experienced a grade 3 abdominal infection. Patient 3 exhibited only a grade 1 elevation in liver enzymes.

Discussion

Approximately 50% of adult T-ALL patients relapse within 1 year after achieving remission, with retreatment remission rates of only 30–45%. Due to the current lack of effective standardized first-line treatment regimens, novel therapeutic strategies are being actively explored worldwide. The Chinese PLA General Hospital adopted a chidamide-combined intensive chemotherapy regimen, achieving a 67.9% CR rate.[9] The MD Anderson Cancer Center (USA) implemented a venetoclax plus Hyper-CVAD – nelarabine – asparaginase regimen, with this cohort demonstrating a 97% ORR and zero early mortality.[10] Additionally, clinical studies of CD7 CAR-T cell therapy have shown remarkable efficacy in T-ALL: among 34 patients, 96% achieved CR with MRD negative status, along with a favorable safety profile.[11]

Compared with conventional chemotherapy, the current regimen demonstrates significantly enhanced efficacy. When benchmarked against emerging therapeutic protocols from other domestic centers, it also exhibits clear advantages. Even when compared with the MD Anderson regimen and CD7 CAR-T clinical outcomes, the present protocol demonstrates comparable efficacy while offering simplified treatment procedures and superior health economics.

The Venetoclax combined with Chidamide and Azacitidine dual epigenetic target regimen is developed based on current research progress in T-ALL pathogenesis. Scientific hypotheses were formulated, followed by the design of cell experiments to verify the efficacy of this regimen, which was ultimately applied in clinical practice demonstrating favorable efficacy and safety outcomes. During the preclinical research stage, the combination of Venetoclax, Chidamide, and Azacitidine exhibited synergistic inhibition effects on Jurkat cells' proliferation, suggesting that this triple-drug combination holds promising potential for T-ALL patients. Five patients treated with this regimen exhibited distinct immunophenotypes, including ND T-ALL and R T-ALL, characterized by high-risk factors such as leukocytosis, high-risk immunophenotype, gene mutations, chromosomal karyotype abnormalities, etc. Although their clinical characteristics varied, all patients showed significant efficacy. The predominant treatment-related adverse events were primarily associated with bone marrow suppression. Notably, in the third patients presenting no significant reduction in blood cell counts at disease onset or throughout the treatment process experienced no hematologic adverse reactions. Conversely, the remaining four patients displayed evident blood cell reduction at onset and encountered severe hematologic toxicity during the initial induction phase; however, they successfully discontinued blood cell transfusions by the second cycle. Furthermore, two patients did not experience bone marrow suppression following T-ALL remission and re-treatment which suggests that the initial induction-associated adverse reactions may not be solely attributed to the disease itself; thus implying that this regimen might only induce mild hematologic toxicity. Overall, the combination of Venetoclax with Chidamide and Azacitidine regimen rapidly achieves deep remission in both ND-TALL and R T-ALL patients while serving as a bridge to stem cell transplantation; additionally, it exhibits good tolerability along with manageable adverse reactions, making it an optimal therapeutic option for high-risk T-ALL individuals.

The combination of Venetoclax with Chidamide and Azacitidine regimen represents the initial endeavor to shift the treatment approach for T-ALL from intensive chemotherapy to non-chemotherapeutic methods. Currently, the treatment of T-ALL still adheres to the same chemotherapy regimens as B-cell ALL, employing glucocorticoids, vincristine, L-asparaginase, and anthracyclines as main induction therapy drugs.[12] Given T-ALL's resistance to drugs during induction remission, clinical practice typically employs high-intensity induction therapy in early stages with the aim of significantly reducing tumor burden in the short term and enhancing the success rate of induction therapy. However, despite the use of high-intensity chemotherapy, the success rate of induction remission in T-ALL remains low while also increasing the incidence of adverse reactions. T-ALL and B-ALL exhibit significant differences in cellular biology and molecular characteristics. Traditional regimens cannot fully target specific molecular targets and biological characteristics of T-ALL, limiting drug efficacy and potentially accelerating drug resistance development leading to treatment failure and increased risk of relapse. The induction therapy drugs used in this regimen mainly consist of targeted drugs that selectively kill T-ALL cells by targeting BCL-2 apoptotic protein and epigenetic targets. This approach enhances efficacy

while minimizing risks associated with traditional chemotherapy drugs such as cardiac toxicity, neurotoxicity, liver damage, or kidney damage.

The combination of venetoclax with Chidamide and Azacitidine represents the first instance of utilizing two epigenetic modifiers in conjunction with a BCL-2 inhibitor for the induction therapy of T-ALL. In T-ALL, aberrant methylation of previously unmethylated CpG islands (CGIs) leads to the inactivation of tumor suppressor genes, thereby promoting tumor cell proliferation. Previous studies on mouse models and T-ALL cell lines have identified alterations in the expression levels of key DNA methyltransferases in T-ALL, which may be associated with a potential hypermethylated CGI phenotype observed in T-ALL patients.[13] Research conducted by Alexander Meissner's German team revealed elevated levels of abnormal methylation not only in T-ALL but also in acute myeloid leukemia (AML), through comprehensive genomic analysis involving a large cohort comprising B-cell progenitors, T-lineage ALL samples, corresponding cell lines, and healthy controls. Further investigation indicated a correlation between overall methylation levels and hypermethylation specifically at CGIs in T-ALL, suggesting that an increased state of genomic methylation serves as a hallmark feature for this disease.[14] Reduced levels of histone acetylation, mediated by HDAC, are prevalent epigenetic abnormalities observed in various cancers. The delicate balance between histone acetylation and deacetylation plays a crucial role in determining the transcriptional activity of genes. Histones serve as the protein scaffold of chromatin, where histone acetylation promotes chromatin relaxation and facilitates gene transcription; however, HDAC removes acetyl groups from histones, leading to disruption of chromatin structure and inhibition of transcription for genes involved in tumorigenesis.[15,16] Notably, studies have reported increased expression levels and enhanced activity of HDAC in T-cell acute lymphoblastic leukemia (T-ALL), with HDAC inhibitors demonstrating apoptosis-inducing effects on both T-ALL cell lines and primary cells derived from T-ALL patients.[17] These findings highlight the potential therapeutic value of targeting epigenetic modifications for treating T-ALL. The Bcl-2 protein family serves as critical regulators of apoptosis primarily through activation of the mitochondrial apoptotic pathway to induce cell death. BH3 profiling represents a novel approach for identifying disruptions within this apoptotic pathway by accurately assessing BCL-2 dependency and predicting responses to BCL-2 antagonists. Analysis using BH3 profiling has revealed widespread expression of BCL-2 across both B-cell acute lymphoblastic leukemia (B-ALL) and T-cell ALL cell lines; however, differential expression patterns exist among distinct subgroups within T-ALL that vary with different stages of T-cell differentiation. Notably, high expression levels of BCL-2 have been observed in immature forms of T-cell ALL (ETP–ALL), indicating their heightened sensitivity to venetoclax treatment.[18,19] Bcl-2 represents a promising therapeutic target for patients with T-cell acute lymphoblastic leukemia (T-ALL). The efficacy of venetoclax combination therapy has been demonstrated in several small-scale studies specifically in early T-cell precursor ALL (ETP-ALL), while its effectiveness is limited in non-ETP-ALL cases.[20–23] However, both ETP and non-ETP patients have shown remarkable response rates following the addition of dual epigenetic inhibitors, suggesting the potential applicability of this treatment regimen across different subtypes. Currently, guideline recommendations endorse regimens based on idarubicin for refractory T-ALL management. Preclinical investigations have validated that combining idarubicin with DNMTs such as decitabine can effectively eliminate T-ALL cells by reducing cell viability and inducing apoptosis.[24] The combination of idarubicin and venetoclax effectively inhibits the proliferation of T-ALL cell lines and induces apoptosis, while significantly downregulating the expression and phosphorylation of PI3K and AKT.[25] Cytarabine reduces the levels of anti-apoptotic protein MCL-1, synergistically combating leukemia when combined with venetoclax, disrupting leukemia cell metabolism, and eliminating leukemia stem cells. This drug combination holds potential for inducing deep remission in T-ALL.[26] Based on these findings, it is hypothesized that combining idarubicin with venetoclax and cytarabine represents a feasible strategy for treating T-ALL, forming the theoretical basis for an improved dual epigenetic multi-target clinical regimen centered around "idarubicin + cytarabine" as dual epigenetic modifiers combined with the BCL-2 inhibitor venetoclax. In vitro experiments further confirm the synergistic effects of this three-drug combination, demonstrating its efficacy and safety in clinical use.

Currently, the efficacy of this regimen has only been demonstrated in a limited number of patients, which somewhat hampers the generalizability and representativeness of clinical data. Therefore, further large-scale clinical trials are imperative to validate this treatment strategy. Moreover, there is a dearth of data regarding the application of this regimen

in relapsed and refractory T-ALL patients, necessitating additional research to identify specific patient subgroups that may benefit from it and elucidate the cytogenetic and molecular biological characteristics influencing their prognosis.

Ethical Approval

The Institution Review Board (IRB) of the Sichuan Provincial People's Hospital approved this study and all standard ethical guidelines were followed. Approval for the publication of case details was obtained from the same institution.

Consent to Publish

All the detailed clinical data of the patients published in this article were obtained with the consent of the patients themselves.

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Disclosure

No conflict of interest in this paper.

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