JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Impact of Nelarabine on Gene Expression Profiles in T-Cell Acute Lymphoblastic Leukaemia: A Comprehensive Literature

[1]Pooja Kushwah, [2]Dr. Pushpender kumar*, [3]Ranjeet Kumar

[1] PG Scholar, Department of Pharmacology, Faculty of Pharmacy, Uttar Pradesh University of Medical Sciences, Saifai, Etawah 206130, UP, India.

[2]Assistant Professor, Department of Pharmacology, Faculty of Pharmacy, Uttar Pradesh University of Medical Sciences, Saifai, Etawah 206130, UP, India.

[3] PG Scholar, Department of Pharmacology, Faculty of Pharmacy, Uttar Pradesh University of Medical Sciences, Saifai, Etawah 206130, UP, India.

ABSTRACT

T-cell acute lymphoblastic leukaemia (T-ALL) is a formidable hematologic malignancy, noted for its aggressive clinical course and unfavourable prognosis. Nelarabine, a guanine nucleoside analog approved by the FDA in March 2023, has emerged as the sole T-ALL-specific therapeutic agent in clinical use. This compound preferentially accumulates in T-cells, where its active metabolite, ara-G triphosphate, disrupts DNA synthesis and induces apoptosis. Despite its increasing clinical application, a comprehensive understanding of nelarabine's molecular mechanisms and its effects on gene expression profiles in T-ALL remains incomplete. This literature review systematically explores the intracellular metabolism of nelarabine, the molecular pathways it influences, resistance mechanisms, and implications for optimizing therapeutic strategies. Evidence indicates that nelarabine-induced gene expression alterations involve dysregulation of DNA synthesis pathways, apoptotic machinery, and metabolic reprogramming. Emerging research suggests that resistance to nelarabine is associated with changes in drug transporters, phosphorylation enzymes, and anti-apoptotic signaling. Understanding these molecular mechanisms is crucial for identifying patient populations most likely to benefit from nelarabine-based therapy and for developing rational combination strategies to overcome resistance. This review synthesizes current knowledge on nelarabine's effects on T-ALL gene expression and proposes future research directions to enhance treatment efficacy.

Keywords: Nelarabine, T-cell acute lymphoblastic leukemia, gene expression, molecular mechanisms, drug resistance, ara-G triphosphate

1. INTRODUCTION

1.1 T-Cell Acute Lymphoblastic Leukaemia: Clinical Significance and Epidemiology

T-cell acute lymphoblastic leukaemia (T-ALL) accounts for 10-15% of paediatric acute lymphoblastic leukaemia cases and approximately 25% of adult ALL cases [1]. Despite significant advances in chemotherapy regimens over recent decades, T-ALL remains a particularly challenging malignancy with inferior outcomes compared to B-cell precursor ALL. The 5-year event-free survival (EFS) rate in newly diagnosed T-ALL approaches 85% in paediatric patients treated on contemporary protocols, yet this varies significantly based on disease stratification and early treatment response [2]. Adults with T-ALL demonstrate substantially poorer outcomes, with 5-year overall survival rates hovering around 40-50% despite intensive multi-agent chemotherapy [3]. Early T-cell precursor (ETP)-ALL represents a particularly aggressive subtype of T-ALL, characterized by a distinct immunophenotype (CD1a-negative, CD8-negative, CD5-negative/weak, myeloid/stem-cell markers positive) and is associated with 5-year survival rates below 25% [4]. Near-ETP ALL, defined by transcriptional similarity to ETP-ALL but with stronger CD5 expression, exhibits intermediate outcomes, whereas non-ETP T-ALL demonstrates a more favorable prognosis [5].

1.2 Current Treatment Landscape and the Role of Nelarabine

The current approach to treating T-ALL involves the use of intensive multi-agent chemotherapy regimens, which are typically based on augmented Berlin-Frankfurt-Munster (ABFM) protocols or hyper-CVAD combinations. These are often combined with allogeneic stem cell transplantation (allo-SCT) for patients at high risk. While these methods have led to significant improvements in patient outcomes,

treatment failure remains a considerable clinical issue, particularly for those who do not respond to initial treatment or who relapse early [6-9]. The chemotherapy agents used include glucocorticoids, which trigger apoptosis through transcriptional regulation; asparaginase, which reduces asparagine levels and disrupts protein synthesis; nucleoside analogs such as cytarabine; DNA-damaging agents like doxorubicin and etoposide; and targeted therapies. Despite the variety of available treatments, some patients either do not respond or experience disease recurrence, underscoring the need for new therapeutic strategies [10]. The FDA's approval of nelarabine on March 8, 2023, represents a significant advancement in T-ALL treatment [1]. This approval marks the culmination of nearly six decades of research into nelarabine's efficacy in treating high-grade, aggressive T-cell malignancies. As a T-cell-selective agent designed with precision, nelarabine offers unique benefits over traditional chemotherapy by leveraging the specific metabolic traits of T-cells [11].

1.3 Nelarabine: Chemical Structure and Mechanism of Action

Nelarabine is a prodrug of the deoxyguanosine analog ara-G (9-beta-D-arabinofuranosylguanine) [12, 13]. Unlike conventional chemotherapy agents, nelarabine has a remarkable ability to selectively accumulate in T-cells, making it an inherently targeted therapeutic agent. Understanding its therapeutic efficacy and cellular effects hinges on the molecular structure of nelarabine and its conversion to active metabolites [14, 15]. The general mechanism of nelarabine involves cellular uptake through human Equilibrative Nucleoside Transporter 1 (hENT1), intracellular phosphorylation to ara-G triphosphate (ara-GTP), incorporation into nuclear and mitochondrial DNA, and termination of DNA synthesis leading to cell death [16]. This process results in the preferential accumulation of cytotoxic ara-G triphosphate in T-cells compared to B-cells or other hematopoietic cells, explaining the T-cell-specific therapeutic activity. 1.4 Scope and Objectives of This Review This comprehensive literature review examines the molecular mechanisms underlying nelarabine's activity in T-ALL, with particular emphasis on its effects on gene expression profiles. The specific objectives include clarifying the intracellular metabolism of nelarabine and the generation of ara-G triphosphate, delineating the molecular targets and cellular pathways affected by nelarabine treatment, characterizing gene expression changes induced by nelarabine in T-ALL cells, reviewing molecular mechanisms of nelarabine resistance, synthesizing current knowledge regarding nelarabine's clinical efficacy, and identifying future research directions for optimizing nelarabine-based therapy. Could you please provide more specific details or a topic on which you require references and citations? This will help me assist you better.

2. MATERIALS AND METHODS

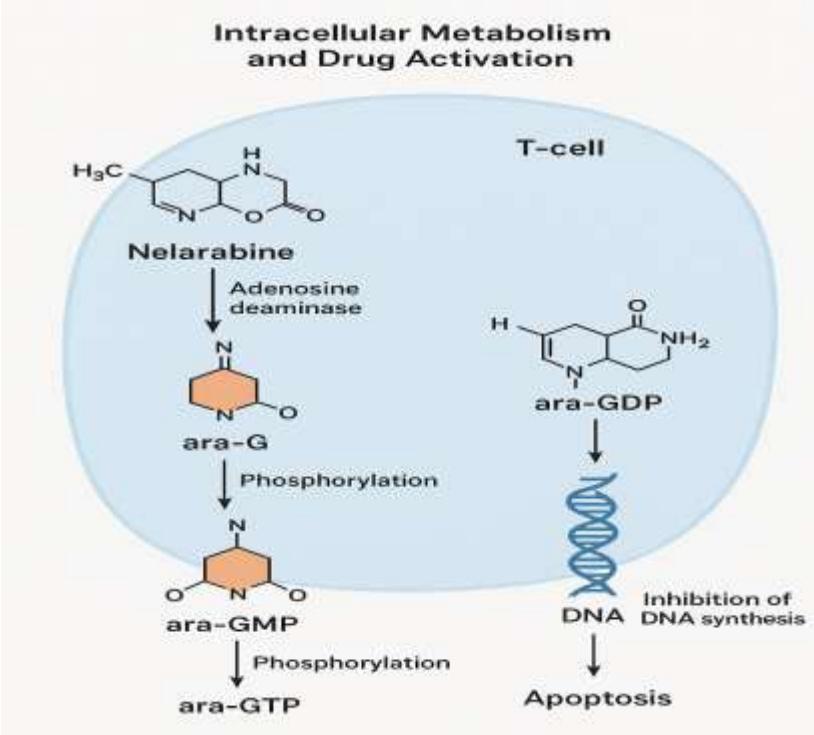
2.1 Literature Search Strategy: A comprehensive literature search was conducted using PubMed/MEDLINE, Google Scholar, and institutional databases up to February 2025. The search queries employed included "Nelarabine gene expression T-ALL," "Ara-G metabolism acute lymphoblastic leukemia," "T-cell acute lymphoblastic leukemia molecular pathways," "Nelarabine DNA synthesis apoptosis," "Drug resistance T-ALL mechanisms," "Early T-cell precursor ALL," and "Nucleoside analog ara-G."

2.2 Inclusion and Exclusion Criteria Inclusion Criteria: Primary research articles, clinical trials, and reviews focusing on nelarabine or Ara-G in leukemia; studies examining gene expression profiles in T-ALL; investigations of nelarabine resistance mechanisms; clinical outcome studies incorporating nelarabine in T-ALL treatment protocols; mechanistic studies of nucleoside analog pharmacology in T-cells; peer-reviewed publications in English. Exclusion Criteria: Case reports with fewer than three patients; non-peer-reviewed sources; studies not directly relevant to T-ALL or nelarabine; publications predating 1995; articles lacking sufficient methodological detail.

2.3 Data Extraction and Analysis From each included article, the following information was systematically extracted: Study Design: Type of study (clinical trial, preclinical, mechanistic); Patient/Cell Population: Sample size, age range, disease characteristics; Molecular Findings: Gene expression changes, affected pathways, molecular mechanisms; Clinical Outcomes: Response rates, survival data, disease-free survival; Methodologies: Techniques employed (RNA-seq, microarray, Western blotting, qRT-PCR); Key Conclusions: Primary findings and their relevance to the mechanism of action of nelarabine. 2.4 Quality Assessment The quality of the included studies was assessed using the following criteria: sample size and statistical power; appropriate control groups; validation of findings in independent cohorts; relevance of methodology to clinical application; clarity of statistical analysis; and disclosure of potential conflicts of interest.

3. MOLECULAR PHARMACOLOGY OF NELARABINE

3.1 Intracellular Metabolism and Drug Activation: A comprehensive understanding of nelarabine's molecular pharmacology is vital for appreciating its influence on gene expression. Nelarabine serves as a prodrug, undergoing a series of phosphorylation steps to form its active metabolite, ara-G triphosphate (ara-GTP) [17, 18]. Unlike many chemotherapy drugs that indiscriminately target rapidly dividing cells, nelarabine exhibits a preference for T-cells due to the distinct expression of metabolic enzymes and transporters [13, 18]. The metabolic pathway involves: Cellular Uptake: Nelarabine is primarily taken up by cells through hENT1, a nucleoside transporter with a strong affinity for purine analogs. Initial Phosphorylation: The prodrug is enzymatically converted, although the specific enzymes and initial activation steps remain to be fully elucidated. ara-G Generation: The active nucleoside ara-G is generated within the cell. Sequential Phosphorylation: ara-G is phosphorylated in sequence to ara-G monophosphate, ara-G diphosphate, and ultimately ara-G triphosphate (ara-GTP), facilitated by both cytosolic deoxycytidine kinase (dCK) and mitochondrial deoxyguanosine kinase (dGK) [20]. Ara-GTP is the main active metabolite responsible for the drug's anti-leukemic effects [21]. The triphosphate metabolite accumulates more in T-cells than in other hematopoietic cell types, accounting for its selective action against T-ALL [22].



3.2 Mechanisms of Cytotoxicity: DNA Synthesis Inhibition The primary mechanism by which nelarabine induces cell death is through the incorporation of ara-GTP into nuclear and mitochondrial DNA, resulting in the cessation of DNA synthesis [16, 22]. This mechanism differentiates nelarabine from glucocorticoids and other agents that trigger apoptosis via different pathways. DNA Incorporation and Chain Termination: When ara-GTP is incorporated into a growing DNA strand, it acts as a chain terminator due to its arabinose sugar moiety, which blocks the addition of further nucleotides. This mechanism is similar to that of ara-C (cytarabine) but with nucleotide selectivity specific to guanine positions [24]. Dual DNA Compartment Involvement: Unlike many nucleoside analogs that primarily affect nuclear DNA, nelarabine-induced ara-GTP accumulates in both nuclear and mitochondrial DNA fractions. Studies using tritiated thymidine incorporation have shown that ara-G inhibits DNA synthesis in both compartments, leading to a broad disruption of cellular DNA metabolism [16, 25].

3.3 Apoptosis Induction and Programmed Cell Death Pathways: Beyond the direct inhibition of DNA synthesis, nelarabine treatment initiates programmed cell death by activating apoptotic pathways. The molecular mechanisms behind nelarabine-induced apoptosis involve multiple interconnected signaling cascades: Intrinsic Apoptotic Pathway Activation: DNA damage caused by ara-GTP incorporation triggers the intrinsic apoptotic pathway, marked by mitochondrial permeabilization, cytochrome c release, and caspase activation. Mitochondrial-targeted ara-GTP is particularly significant, as the inhibition of mitochondrial DNA synthesis may provoke mitochondrial stress responses [13, 18, 19]. Differential Apoptotic Sensitivity: Research has revealed variability in apoptotic responses among T-ALL cells to nelarabine. Some populations show strong activation of caspase-3 and poly(ADP-ribose) polymerase (PARP) cleavage following nelarabine exposure, while others display resistance linked to the upregulation of anti-apoptotic proteins [24, 26-29].

4. NELARABINE-INDUCED CHANGES IN GENE EXPRESSION

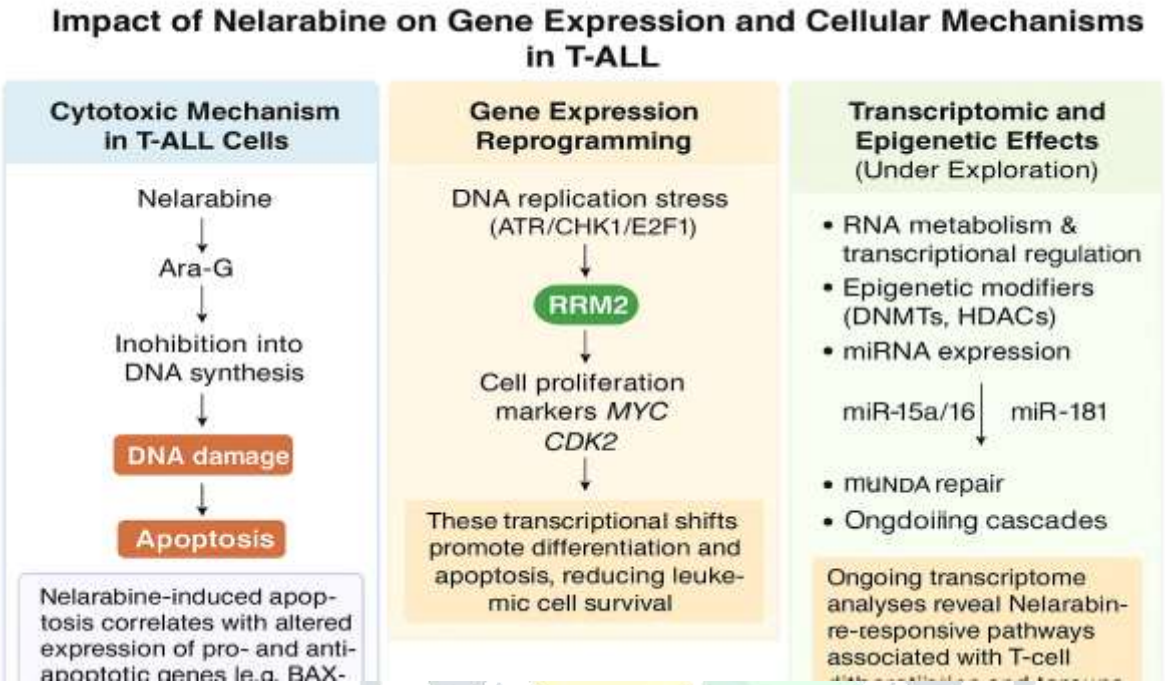
4.1 Genes Involved in DNA Metabolism and Synthesis: Gene expression in T-ALL cells, especially those involved in DNA replication, repair, and synthesis, is significantly impacted by nelarabine therapy. Studies using RNA sequencing and microarray technology have found numerous significant changes: DNA Synthesis Gene Downregulation: Genes encoding DNA polymerases, deoxyribonucleotide synthases, and other DNA replication machinery exhibit decreased expression after being exposed to nelarabine. This downregulation, which reflects cellular stress responses, most likely serves as a compensation mechanism for DNA damage and suppression of DNA synthesis [18, 30, 31]. The activation of the replication stress response results in the upregulation of genes related to the cellular reaction to replication fork stalling and DNA damage checkpoints. Activation of the G1/S and G2/M cell cycle checkpoints is reflected by these p53-target genes, which include p21 (CDKN1A) and BAX [10].

4.2 Apoptosis-Related Gene Expression Changes: Apoptotic regulatory genes, both pro- and anti-apoptotic, are significantly dysregulated as a result of nerarabine-induced changes in gene expression. Expression of Pro-Apoptotic Genes: In susceptible T-ALL cells, nelarabine exposure causes an increase in the expression of pro-apoptotic genes such as BAX, PUMA, and NOXA. The involvement of mitochondrial apoptotic pathways is reflected in these modifications. Gene Modulation to Prevent Apoptosis: Ironically, resistant T-ALL cell types have either preserved or elevated expression of anti-apoptotic proteins like MCL-1, BCL-2, and BCL-XL. This pattern of gene expression is a crucial resistance mechanism that enables cells to withstand DNA damage and avoid nelarabine-induced apoptosis [16, 32].

4.3 Glucocorticoid-Associated Gene Expression Programs: Remarkably, research comparing the gene expression of T-ALL cells that are nelarabine-sensitive and -resistant has found correlations with glucocorticoid responsiveness pathways: Expression of

Glucocorticoid Receptors (GR);In some T-ALL subtypes, sensitivity to both glucocorticoids and nelarabine is correlated with the expression level of the glucocorticoid receptor (NR3C1). High-GR expression cells react more apoptotically to medication ([10]. Target Genes of Downstream Glucocorticoids, Some nelarabine-responsive T-ALL cells have increased expression of glucocorticoid-inducible genes (e.g., FKBP5, TSC22D3), according to gene expression profiling, indicating a relationship between glucocorticoid signaling and the nelarabine-induced DNA damage response [1].

4.4 Metabolic Gene Expression Reprogramming: Recent studies have shown that nelarabine therapy results in significant alterations in metabolic gene expression: Oxidative Phosphorylation Alterations: Dysregulation of oxidative phosphorylation (OxPhos) pathway genes is revealed by gene expression profiling following nelarabine exposure. Genes encoding Complex I, II, III, and IV subunits have changed expression, which may indicate reactions to mitochondrial stress. Genes for Amino Acid Metabolism: Amino acid metabolic enzymes, especially those involved in asparagine synthesis (ASNS), glutamine metabolism, and branched-chain amino acid (BCAA) metabolism, are frequently upregulated in nelarabine-resistant cells. Survival despite drug exposure is made possible by this metabolic reprogramming [33-38].



5. RESISTANCE MECHANISMS: MOLECULAR BASIS AND GENE EXPRESSION ALTERATIONS

5.1 Nucleoside transporter failure is one of the best-characterised causes of nelarabine resistance. It also contributes to drug uptake resistance. Down-regulating hENT1: SLC29A1 (hENT1), the main nelarabine transporter, had much lower transcript levels in nelarabine-resistant cell types [39, 40]. With resistant cells accumulating only 25% of the ara-GTP levels seen in sensitive cells despite similar drug exposure, this reduction in gene expression results in significantly reduced drug uptake. The degree of hENT1 expression at diagnosis may be a predictor of nelarabine drug sensitivity or resistance, according to research using transporter gene expression as a predictive biomarker. Nelarabine-based treatment is more effective in patients whose leukemic cells display higher amounts of hENT1 [13].

5.2 Phosphorylation Enzyme Deficiency: Resistance usually entails decreased expression or function of important phosphorylation enzymes in addition to transporter dysfunction: Kinases for deoxycytidine (dCK) and deoxyguanosine (dGK) expression: The primary enzymes that catalyze ara-G phosphorylation, dCK and dGK, are both significantly down-regulated in nelarabine-resistant T-ALL cells [16]. Comparing this reduction to sensitive cells, intracellular ara-GTP accumulation is reduced by 40–50%. Analysis of Gene Expression Profiles: Coordinated downregulation of genes involved in nucleotide metabolism, such as DCK, DGK, and related salvage pathway enzymes, is revealed by RNA sequencing of resistant versus susceptible T-ALL cells [13].

5.3 Anti-Apoptotic Signalling Pathway Activation: Gene expression profiling has identified anti-Apoptotic Signalling Pathway Activation: Nelarabine-resistant T-ALL has been found to activate multiple anti-apoptotic pathways, according to gene expression profiling: The PI3K/AKT/mTOR Pathway Activation of Hyperactivity: The PI3K pathway components and phospho-AKT levels are often upregulated in resistant T-ALL cells, which inhibits pro-apoptotic signaling. AKT kinase transcripts and associated pathway elements are upregulated, according to gene expression analysis [16]. Anti-apoptotic Programs Driven by NOTCH1: A distinctive gene expression pattern of T-ALL with activating NOTCH1 mutations includes increased mTOR signaling and overexpression of downstream target genes (HES1, DELTEX1). Several anti-leukemic drugs, notably nelarabine, are resistant to this NOTCH1-driven program [41]. MDM2-p53 Disruption and Akt Activation: Despite DNA damage, gene expression analyses in nelarabine-resistant cells show decreased p53 pathway activation and elevated MDM2 expression. This is a crucial way to avoid apoptosis [24], which identified several anti-apoptotic pathways activated in nelarabine-resistant T-ALL:

Hyperactivation of the PI3K/AKT/mTOR Pathway: Increased phospho-AKT levels and activation of PI3K pathway components, which inhibit pro-apoptotic signaling, are common features of resistant T-ALL cells. AKT kinase transcripts and associated pathway components are upregulated, according to gene expression analysis [16]. Anti-Apoptotic Programs Driven by NOTCH1: The distinctive gene expression pattern of T-ALL with activating NOTCH1 mutations includes increased mTOR signaling and overexpression of downstream target genes (HES1, DELTEX1). Resistance to several anti-leukemic drugs, including nelarabine, is conferred by this NOTCH1-driven program [41]. Akt Activation and MDM2-p53 Disruption: Despite DNA damage, gene expression analyses in nelarabine-resistant cells show decreased p53 pathway activation and elevated MDM2 expression. A crucial defense against apoptosis is represented by this [24].

5.4 Chromatin remodeling and epigenetic modifications: New data indicates that via changing gene expression patterns, epigenetic modifications may be a factor in nelarabine resistance. Ineffective PRC2 Complex: Polycomb repressive complex 2 (PRC2) components (EZH2, EED, and SUZ12) have been shown to have loss-of-function mutations in chemotherapy-resistant T-ALL. Mutations of this type impact the expression of genes that regulate mitochondrial apoptosis and change chromatin-based transcriptional repression [43].

6. CLINICAL EFFICACY AND PROGNOSTIC IMPLICATIONS

6.1 Nelarabine in Newly Diagnosed T-ALL: The pivotal Children's Oncology Group (COG) AALL0434 trial established the clinical benefit of incorporating nelarabine into front-line T-ALL therapy. This large, randomized trial enrolled 1,562 evaluable patients with T-ALL aged 1-31 years [42].

Disease-Free Survival Improvement: Patients randomized to receive six 5-day courses of nelarabine as part of augmented Berlin-Frankfurt-Munster (ABFM) therapy demonstrated significantly improved 5-year disease-free survival (DFS) rates: 88.2% (with nelarabine) versus 82.1% (without nelarabine), p=0.029 [42]. The most favorable outcomes were observed with the combination of escalating-dose methotrexate without leucovorin rescue plus pegaspargase and nelarabine, achieving 91% 5-year DFS.

CNS Leukemia Reduction: A particularly significant finding was the substantial reduction in isolated and combined CNS relapses in nelarabine-treated patients: 1.3% versus 6.9% (p=0.0001). This suggests nelarabine possesses favorable CNS penetration or enhances CNS-directed prophylaxis efficacy [44].

Toxicity Profile: Importantly, the addition of nelarabine did not significantly increase overall toxicity compared to chemotherapy alone, including neurotoxicity—a dose-limiting side effect of nelarabine when used as salvage therapy [42].

6.2 CNS Status and Prognosis in T-ALL: Analysis of more than 2,000 T-ALL patients who were enrolled in two consecutive COG studies (AALL0434 and AALL1231) showed that the outcome is greatly impacted by CNS involvement upon diagnosis: Status Impact on CNS-3: Individuals with overt CNS leukemia (CNS-3 status), which is defined as having ≥5 white blood cells/μL with blasts in the cerebrospinal fluid and clinical symptoms, had much worse outcomes: their 4-year event-free survival (EFS) was 71.8%, while that of CNS-1 was 85.1% (p=0.0004) and that of CNS-2 was 83.2% (p=0.0004). [45]. Nelarabine Benefit in CNS-3 Disease: Although CNS-3 status is linked to a poor prognosis, nelarabine treatment seemed to offer a selective advantage in this high-risk group. Although CNS-3 patients still showed worse outcomes than CNS-1/2 patients, nelarabine incorporation resulted in a considerable improvement in 4-year disease-free survival [46, 47].

6.3 In relapsed or resistant T-ALL, nerarabine: The sole FDA-approved salvage medication with particular anti-leukemic action for relapsed or refractory (R/R) T-ALL is nelarabine: Reaction Rates in R/R Illness: Nelarabine salvage therapy has been shown to provide overall response rates of about 50% and full remission rates of about 36-43% in adult patients with R/R T-ALL [48]. With a 5-year survival rate of less than 20%, R/R T-ALL has previously had poor results; therefore, these response rates are impressive. Differential responses according to the kind of relapse were found in the German Multicenter ALL Study Group (GMALL) analysis of hematologic versus molecular relapse outcomes. While molecular relapse patients showed significantly lower molCR rates of only 29%, hematologic relapse patients attained CR rates of 48% with nelarabine, indicating that resistance mechanisms vary by type of relapse [49]. The transition to transplantation: Notably, salvage therapy based on nelarabine is a successful stopgap measure before allogeneic stem cell transplantation. Forty percent of people who received nelarabine salvage went on to have SCT, and overall survival after SCT was 46% at two years and 38% at five years [48, 50, 51].

Response of Nelarabine and ETP-ALL The prognosis for early T-cell precursor ALL has historically been dismal, making it a particularly difficult subtype of T-ALL. Comparing the effectiveness of nelarabine in ETP-ALL and non-ETP illnesses showed significant differences in responses: Unique Nelarabine Advantage: The addition of nelarabine to hyper-CVAD therapy was found to improve survival only in non-ETP ALL patients in the analysis by Morita et al. (5-year OS 83% with hyper-CVAD+nelarabine versus 51% with hyper-CVAD alone, p = 0.001). Nelarabine monotherapy, on the other hand, showed no effect for ETP-ALL patients, whereas allo-SCT improved their subpar initial results [4, 5].

7. MOLECULAR MECHANISMS UNDERLYING DIFFERENTIAL NELARABINE RESPONSE

7.1 Gene Expression Signatures Specific to Subtypes: Recent studies show that different gene expression signatures predict nelarabine responsiveness in T-ALL molecular subtypes: T-ALL Mutated by NOTCH1: Increased Notch signaling is reflected in the distinctive gene expression signature of T-ALL with activating NOTCH1 mutations (55–60% of cases). Notch1-driven metabolic reprogramming toward oxidative phosphorylation (OxPhos) promotes survival and may lead to nelarabine resistance unless paired with OxPhos inhibitors, according to recent research [52–54]. Disease of NOTCH1-Wild Type: On the other hand, PTEN deletions, IL7R activating

mutations, and other PI3K/AKT pathway changes are frequently found in NOTCH1-wild-type T-ALL. Different chemotherapeutic sensitivities, including varying nelarabine responses, are displayed by these genetically diverse subgroups. [10]

7.2 Blasts that resemble bone marrow progenitor (BMP) and resistance to treatment: There is a subgroup of bone marrow progenitor-like (BMP-like) leukemia linked to poor survival and treatment failure, according to a recent multiomic study of T-ALL patient data. The following characteristics define the unique gene expression signature of this subpopulation: Gene Expression Progenitor Program: BMP-like blasts overexpress genes like CD34, CD133, and HOXA cluster genes that are normally only seen in hematopoietic progenitors. A poor prognosis and treatment resistance are linked to this progenitor-like gene expression pattern, irrespective of the T-ALL subtype. [55–57]. Venetoclax. BMP-Like Blast Sensitivity Level: Curiously, apoptosis-inducing drugs (venetoclax) were discovered as possible therapeutic weaknesses by in vitro and in silico drug screening, although BMP-like blasts show resistance to traditional chemotherapy, including nelarabine. This implies that BMP-like blast-targeting combination techniques could overcome the resistance to conventional therapy. [55, 58].

7.3 Mitochondrial Dysfunction and Alterations in Metabolic Gene Expression: In T-ALL, mitochondrial dysfunction becomes a significant factor in determining treatment resistance. 284 mitochondrial dysfunction-related differentially expressed genes (MDRDEGs) were found in pediatric T-ALL by gene expression analysis of mitochondrial dysfunction-related genes (MDRGs): Pathway Enrichment for KEGG: These genes were mostly involved in the formation of protein complexes necessary for energy production, oxidative phosphorylation, and the inner membrane of the mitochondria. The NF-κB and JAK-STAT pathways were found to be significantly involved in the drug-resistant phenotype by enrichment analysis. Diagnostic Model Development Two key genes linked to mitochondrial dysfunction, RNLS and ULK1, were found to be high-impact biomarkers predictive of T-ALL diagnosis and response to treatment using machine learning techniques (LASSO regression and random forest algorithms) [59].

8. NOVEL COMBINATION STRATEGIES AND FUTURE DIRECTIONS

8.1 Methods of Rational Combination: Several logical combination tactics have been put forth, building on knowledge of the molecular mechanisms and resistance pathways of nelarabine: PI3K/mTOR Pathway Inhibition: In preclinical models and ex vivo testing, nelarabine and selective PI3K inhibitors (like ZSTK-474) have synergistic effects due to the frequent hyperactivation of the PI3K/AKT/mTOR pathway in nelarabine-resistant T-ALL. The combination overcomes nelarabine resistance by causing significant AKT dephosphorylation and downregulating anti-apoptotic BCL-2 [60]. CXCR4 Blockade: Nelarabine and the CXCR4 antagonist BL-8040 together showed encouraging activity in R/R T-ALL clinical study results (NCT02763384). In contrast to nelarabine's inhibition of DNA synthesis, CXCR4 blockage appears to mechanistically lower mitochondrial mass and cause non-apoptotic cell death through metabolic disturbance [61]. Inhibition of Oxidative Phosphorylation (OxPhos): Nelarabine and the complex I inhibitor IACS-010759 exhibit notable preclinical effectiveness in treating T-ALL with a NOTCH1 mutation. Leukemic cell death results from the combination's induction of an energy crisis, which is marked by a reduction in the oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) [41].

8.2. ACHM-025 as an Innovative Nelarabine Substitute: ACHM-025, a prodrug preferentially activated by the enzyme AKR1C3 (aldo-keto reductase family 1 member C3), has been discovered via recent preclinical research. In T-ALL PDX models, this drug has impressive activity: Better Performance of Nelarabine in Comparison: Nelarabine as a single drug was significantly less efficacious than ACHM-025 in direct comparisons (median time to event: 19 versus 198 days, p=0.0005). Most astonishingly, when ACHM-025 and nelarabine were used together to treat chemoresistant T-ALL PDXs in vivo, no relapse was seen more than 250 days after treatment. AKR1C3 as a Biomarker for Prediction: AKR1C3 expression is noticeably higher in T-ALL than in B-cell ALL. A predictive biomarker of ACHM-025 efficacy was AKR1C3 expression, and T-ALL PDXs with high AKR1C3 expression showed better responses than those with low AKR1C3 [62].

8.3 Understanding and Overcoming Nelarabine-Specific Toxicities: While nelarabine offers therapeutic advantages in T-ALL, dose-limiting neurotoxicity remains a significant clinical challenge, particularly in salvage settings. Understanding the molecular basis of nelarabine neurotoxicity is critical for optimizing dosing strategies. Neurotoxicity Mechanisms: Nelarabine-induced neurotoxicity likely results from ara-GTP accumulation in neural cells, causing DNA synthesis inhibition and neuronal apoptosis. Peripheral neuropathy, manifesting as paresthesias and motor weakness, represents the most common manifestation. Central nervous system toxicity, including encephalopathy and leukoencephalopathy, occurs in more severe cases, particularly with high cumulative doses [13].

9. CURRENT KNOWLEDGE GAPS AND FUTURE RESEARCH DIRECTIONS

9.1 Essential Clarifications on Nelarabine Pharmacology: The molecular mechanisms behind nelarabine have been studied for decades; however, numerous basic concerns remain unanswered: Types of DNA Damage and Repair: It is still unknown how exactly nelarabine-induced DNA lesions and the cellular repair mechanisms are described, even if ara-GTP incorporation into DNA results in chain termination. It is still unclear if lesions caused by nelarabine cause DNA damage response pathways that are different from those caused by traditional chemotherapy and if resistance is influenced by repair mechanisms. Beyond DNA Synthesis: According to recent research, nelarabine's effects may affect more than just DNA synthesis. There is still more research needed to determine how nelarabine metabolites affect the creation of proteins, RNA, or epigenetic changes [13].

9.2 Development of Biomarkers for Treatment Selection: A crucial therapeutic need is the creation of predictive biomarkers to determine which patients will benefit most from nelarabine therapy in the future. Expression Signature Panels: Extensive gene expression profiling research ought to uncover minimum gene panels whose expression indicates susceptibility to nelarabine. Potential candidates include metabolic genes, hENT1, dCK, dGK, anti-apoptotic genes (BCL-2, MCL-1), and NOTCH1 mutation status [13].

Application of single-cell protein and RNA profiling to nelarabine-treated T-ALL has the potential to detect resistance mechanisms and cell-state-specific responses that are not visible in bulk population analysis [55].

9.3 Mechanisms of Mitochondrial Involvement: Additional research is necessary to understand the effects of inhibiting mitochondrial DNA synthesis and the differential incorporation of ara-GTP into mitochondrial versus nuclear DNA. Studies on Mitochondrial DNA Depletion: A thorough examination of whether nelarabine cytotoxicity is aggravated by mitochondrial DNA depletion may indicate whether nelarabine efficacy is increased by mitochondrial-targeted treatments [63]. During Nelarabine Treatment, Metabolic Reprogramming: Extensive metabolomic research investigating the effects of nelarabine-induced DNA damage on cellular metabolism, including OxPhos capacity, glycolytic activity, and amino acid metabolism, would reveal metabolic weaknesses that could be taken advantage of with combination therapy [13].

9.4 Combination Therapy Optimization: While several rational combination strategies have been proposed, systematic investigation comparing different combination approaches is necessary: **Sequential versus Simultaneous Administration:** Clinical trials examining optimal timing and sequencing of nelarabine with other agents could identify superior treatment schedules [60]. **Patient Population Selection:** Prospective studies utilizing molecular profiling to select patient populations most likely to benefit from specific nelarabine combinations could improve therapeutic outcomes [10, 64, 65].

10. CONCLUSION

Nelarabine represents a significant therapeutic advance for T-ALL, offering T-cell-selective activity and incorporation into both pediatric and adult treatment protocols. This comprehensive literature review synthesizes current knowledge regarding nelarabine's molecular mechanisms, effects on gene expression profiles, resistance mechanisms, and clinical efficacy.

Key findings include: Molecular Mechanism: Nelarabine, through its active metabolite ara-GTP, inhibits DNA synthesis by incorporation into nuclear and mitochondrial DNA, triggering apoptotic cell death through intrinsic pathways. Gene Expression Changes: Nelarabine treatment induces characteristic alterations in genes controlling DNA metabolism, apoptosis regulation, and metabolic pathways. Sensitive cells demonstrate upregulation of pro-apoptotic genes and downregulation of anti-apoptotic factors, while resistant cells maintain or increase anti-apoptotic gene expression. Resistance Mechanisms: Nelarabine resistance involves multifactorial changes, including reduced hENT1 expression (limiting drug uptake), decreased phosphorylation enzyme activity (dCK, dGK), anti-apoptotic signaling pathway hyperactivation (particularly via PI3K/AKT and NOTCH1), and epigenetic modifications affecting chromatin-based transcriptional control. Clinical Efficacy: Incorporation of nelarabine into front-line T-ALL therapy improves disease-free survival and reduces CNS relapse. As salvage therapy for R/R T-ALL, nelarabine achieves 36-43% complete remission rates and effectively bridges patients to allogeneic stem cell transplantation. Future Opportunities: Emerging evidence supports rational combination strategies, including PI3K inhibition, CXCR4 blockade, and OxPhos inhibition. Development of predictive biomarkers to identify responsive patients and investigation of novel agents with complementary mechanisms (such as ACHM-025) represent promising avenues for further improving outcomes.

Understanding the molecular basis of nelarabine's activity and resistance mechanisms provides the foundation for optimizing its clinical application and developing superior therapeutic strategies. Future research integrating molecular profiling, functional genomics, and systematic combination studies will further enhance the precision treatment of T-ALL and improve patient outcomes.

REFERENCES

1. Miller, L. H., Maxa, K. L., Winter, S. S., & Gossai, N. P. (2023). The role of nelarabine in the treatment of T-cell acute lymphoblastic leukemia/lymphoma: challenges, opportunities, and future directions. *Expert Review of Anticancer Therapy*, *23*(12), 1229-1236.
2. Imai, C., Hatta, Y., Sato, A., Oshima, K., Okamoto, Y., Deguchi, T., ... & Horibe, K. (2024). Prognostic Factors for T-Cell Acute Lymphoblastic Leukemia in Children and Young Adults: The ALL-T11 Study Conducted by the Japan Children's Cancer Group and the Japan Adult Leukemia Study Group. *Blood*, *144*, 1426.
3. Jabbour, E., O'Brien, S., Konopleva, M., & Kantarjian, H. (2015). New insights into the pathophysiology and therapy of adult acute lymphoblastic leukemia. *Cancer*, *121*(15), 2517-2528.
4. Morita, K., Kantarjian, H. M., Fang, H., Ravandi, F., Jain, N., Konopleva, M., ... & Jabbour, E. (2020). Outcome of patients with T-cell acute lymphoblastic leukemia/lymphoma with early T-cell precursor-like immunophenotype with strong CD5 expression. *Blood*, *136*, 38-40.
5. Morita, K., Jain, N., Kantarjian, H., Takahashi, K., Fang, H., Konopleva, M., ... & Jabbour, E. (2021). Outcome of T-cell acute lymphoblastic leukemia/lymphoma: focus on near-ETP phenotype and differential impact of nelarabine. *American Journal of Hematology, 96*(5), 589-598.
6. Koenig, R. (2006). The legacy of great science: the work of Nobel Laureate Gertrude Elion lives on. *The Oncologist*, *11*(9), 961-965.
7. Kurtzberg, J. (2007). The long and winding road of the clinical development of Nelarabine. *Leukemia & lymphoma*, *48*(1), 1-2.
8. Zhang, J., Ding, L., Holmfeldt, L., Wu, G., Heatley, S. L., Payne-Turner, D., ... & Mullighan, C. G. (2012). The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. *Nature*, *481*(7380), 157-163.
9. Kisor, D. F., Plunkett, W., Kurtzberg, J., Mitchell, B., Hodge, J. P., Ernst, T., ... & Gandhi, V. (2000). Pharmacokinetics of nelarabine and 9-beta-D-arabinofuranosyl guanine in pediatric and adult patients during a phase I study of nelarabine for the treatment of refractory hematologic malignancies. *Journal of clinical oncology*, *18*(5), 995-995.

10. Follini, E., Marchesini, M., & Roti, G. (2019). Strategies to overcome resistance mechanisms in T-cell acute lymphoblastic leukemia. *International journal of molecular sciences*, *20*(12), 3021.
11. Kisor, D. F. (2009). collaboration to Meet a Therapeutic need: The Development of nelarabine. *Clinical Medicine. Therapeutics*, *1*, CMT-S2909.
12. Cohen, A., Gudas, L. J., Ammann, A. J., Staal, G. E., & Martin, D. W. (1978). Deoxyguanosine triphosphate as a possible toxic metabolite in the immunodeficiency associated with purine nucleoside phosphorylase deficiency. *The Journal of Clinical Investigation*, *61*(5), 1405-1409.
13. Hormann, F. M., & Rudd, S. G. (2025). Nelarabine in T-cell acute lymphoblastic leukemia: intracellular metabolism and molecular mode-of-action. *Leukemia*, 1-12.
14. Shimony, S., DeAngelo, D. J., & Luskin, M. R. (2024). Nelarabine: when and how to use in the treatment of T-cell acute lymphoblastic leukemia. *Blood Advances*, *8*(1), 23-36.
15. Cooper, T. M. (2007). Role of nelarabine in the treatment of T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma. *Therapeutics and Clinical Risk Management*, *3*(6), 1135-1141.
16. Yamauchi, T., Uzui, K., Nishi, R., Shigemi, H., & Ueda, T. (2014). Reduced drug incorporation into DNA and antiapoptosis as the crucial mechanisms of resistance in a novel nelarabine-resistant cell line. *BMC cancer*, *14*(1), 547.
17. Reist, E. J., & Goodman, L. (1964). Synthesis of 9-β-D-arabinofuranosylguanine. *Biochemistry*, *3*(1), 15-18.
18. Cohen, A., Lee, J. W., & Gelfand, E. W. (1983). Selective toxicity of deoxyguanosine and arabinosyl guanine for T-leukemic cells.
19. Mitchell, B. S., Mejias, E., Daddona, P. E., & Kelley, W. N. (1978). Purinogenic immunodeficiency diseases: selective toxicity of deoxyribonucleosides for T cells. *Proceedings of the National Academy of Sciences*, *75*(10), 5011-5014.
20. Yao, S. Y., Ng, A. M., Cass, C. E., Baldwin, S. A., & Young, J. D. (2011). Nucleobase transport by human equilibrative nucleoside transporter 1 (hENT1). *Journal of Biological Chemistry*, *286*(37), 32552-32562.
21. Roecker, A. M., Stockert, A., & Kisor, D. F. (2010). Nelarabine in the treatment of refractory T-cell malignancies. *Clinical Medicine Insights: Oncology*, *4*, CMO-S4364.
22. Verhoef, V., & Fridland, A. (1985). Metabolic basis of arabinonucleoside selectivity for human leukemic T-and B-lymphoblasts. *Cancer research*, *45*(8), 3646-3650.
23. Rodriguez Jr, C. O., Stellrecht, C. M., & Gandhi, V. (2003). Mechanisms for T-cell selective cytotoxicity of arabinosylguanine. *Blood*, *102*(5), 1842-1848.
24. Lonetti, A., Cappellini, A., Bertaina, A., Locatelli, F., Pession, A., Buontempo, F., ... & Chiarini, F. (2016). Improving nelarabine efficacy in T cell acute lymphoblastic leukemia by targeting aberrant PI3K/AKT/mTOR signaling pathway. *Journal of hematology & oncology*, *9*(1), 114.
25. Prus, K. L., Averett, D. R., & Zimmerman, T. P. (1990). Transport and metabolism of 9-β-D-arabinofuranosylguanine in a human T-lymphoblastoid cell line: nitrobenzylthioinosine-sensitive and-insensitive influx. *Cancer research*, *50*(6), 1817-1821.
26. Shigemi, H., Yamauchi, T., Tanaka, Y., & Ueda, T. (2013). Novel leukemic cell lines resistant to clofarabine by mechanisms of decreased active metabolite and increased antiapoptosis. *Cancer science*, *104*(6), 732-739.
27. Imataki, O., Fujita, H., & Uemura, M. (2024). Negative Impact of Gemtuzumab Ozogamicin on CD33-Positive Early T-Cell Precursor Acute Lymphoblastic Leukemia: A Case Report. *Case Reports in Oncology*, *17*(1), 264-269.
28. Rindiarti, A., Okamoto, Y., Nakagawa, S., Hirose, J., Kodama, Y., Nishikawa, T., & Kawano, Y. (2022). Changes in intracellular activation-related gene expression and induction of Akt contribute to acquired resistance toward nelarabine in CCRF-CEM cell line. *Leukemia & Lymphoma*, *63*(2), 404-415.
29. Tsesmetzis, N., Paulin, C. B., Rudd, S. G., & Herold, N. (2018). Nucleobase and nucleoside analogues: resistance and re-sensitisation at the level of pharmacokinetics, pharmacodynamics and metabolism. *Cancers*, *10*(7), 240.
30. Mueller, W. E. G., Geurtsen, W., Beyer, R., Schuster, D. K., Zahn, R. K., & Arendes, J. (1981). Arabinosyl nucleosides. XXXII. Mechanism of inhibition of L5178y mouse lymphoma cells by 9-β-D-arabinofuranosylguanine. *Chemico-Biological Interactions*, *34*(3), 301-313.
31. Shewach, D. S., Daddona, P. E., Ashcraft, E., & Mitchell, B. S. (1985). Metabolism and selective cytotoxicity of 9-β-D-arabinofuranosylguanine in human lymphoblasts. *Cancer research*, *45*(3), 1008-1014.
32. Lonetti, A., Cappellini, A., Bertaina, A., Locatelli, F., Pession, A., Buontempo, F., ... & Chiarini, F. (2016). Improving nelarabine efficacy in T cell acute lymphoblastic leukemia by targeting aberrant PI3K/AKT/mTOR signaling pathway. *Journal of hematology & oncology*, *9*(1), 114.
33. Zhu, C., Johansson, M., Permert, J., & Karlsson, A. (1998). Enhanced cytotoxicity of nucleoside analogs by overexpression of mitochondrial deoxyguanosine kinase in cancer cell lines. *Journal of Biological Chemistry*, *273*(24), 14707-14711.
34. Wang, L., Karlsson, A., Arner, E. S., & Eriksson, S. (1993). Substrate specificity of mitochondrial 2'-deoxyguanosine kinase. Efficient phosphorylation of 2-chlorodeoxyadenosine. *Journal of Biological Chemistry*, *268*(30), 22847-22852.
35. Zhu, C., Johansson, M., Permert, J., & Karlsson, A. (1998). Phosphorylation of anticancer nucleoside analogs by human mitochondrial deoxyguanosine kinase. *Biochemical pharmacology*, *56*(8), 1035-1040.
36. Lewis, R. A., & Link, L. (1989). Phosphorylation of arabinosyl guanine by a mitochondrial enzyme of bovine liver. *Biochemical pharmacology*, *38*(12), 2001-2006.
37. Rodriguez Jr, C. O., Mitchell, B. S., Ayres, M., Eriksson, S., & Gandhi, V. (2002). Arabinosylguanine is phosphorylated by both cytoplasmic deoxycytidine kinase and mitochondrial deoxyguanosine kinase. *Cancer research*, *62*(11), 3100-3105.

38. Cohen, J. D., Strock, D. J., Teik, J. E., Laguardia, E. A., & Katz, T. B. (1999). Clinically relevant deoxycytidine levels are high enough to profoundly alter 9-beta-D-arabinofuranosylguanine cytotoxicity for human T-cell acute leukemia cells in vitro. *Pediatric hematology and oncology*, *16*(3), 239-244.
39. Shigemi, H., Yamauchi, T., Tanaka, Y., & Ueda, T. (2013). Novel leukemic cell lines resistant to clofarabine by mechanisms of decreased active metabolite and increased antiapoptosis. *Cancer science*, *104*(6), 732-739.
40. Yamauchi, T., Negoro, E., Kishi, S., Takagi, K., Yoshida, A., Urasaki, Y., ... & Ueda, T. (2009). Intracellular cytarabine triphosphate production correlates to deoxycytidine kinase/cytosolic 5′-nucleotidase II expression ratio in primary acute myeloid leukemia cells. *Biochemical pharmacology*, *77*(12), 1780-1786.
41. Baran, N., Lodi, A., Dhungana, Y., Herbrich, S., Collins, M., Sweeney, S., ... & Konopleva, M. (2022). Inhibition of mitochondrial complex I reverses NOTCH1-driven metabolic reprogramming in T-cell acute lymphoblastic leukemia. *Nature communications*, *13*(1), 2801.
42. Dunsmore, K. P., Winter, S. S., Devidas, M., Wood, B. L., Esiashvili, N., Chen, Z., ... & Hunger, S. P. (2020). Children's Oncology Group AALL0434: a phase III randomized clinical trial testing nelarabine in newly diagnosed T-cell acute lymphoblastic leukemia. *Journal of Clinical Oncology*, *38*(28), 3282-3293.
43. Kempf, J. M., Weser, S., Bartoschek, M. D., Metzeler, K. H., Vick, B., Herold, T., ... & Spiekermann, K. (2021). Loss-of-function mutations in the histone methyltransferase EZH2 promote chemotherapy resistance in AML. *Scientific reports*, *11*(1), 5838.
44. Gossai, N. P., Devidas, M., Chen, Z., Wood, B. L., Zweidler-McKay, P. A., Rabin, K. R., ... & Teachey, D. T. (2023). Central nervous system status is prognostic in T-cell acute lymphoblastic leukemia: a Children's Oncology Group report. *Blood*, *141*(15), 1802-1811.
45. Menne, T., Slade, D., Savage, J., Johnson, S., Irving, J., Kearns, P., ... & Billingham, L. (2022). Selumetinib in combination with dexamethasone for the treatment of relapsed/refractory RAS-pathway mutated paediatric and adult acute lymphoblastic leukaemia (SeluDex): study protocol for an international, parallel-group, dose-finding with expansion phase I/II trial. *BMJ open*, *12*(3), e059872.
46. Vora, A., Andreano, A., Pui, C. H., Hunger, S. P., Schrappe, M., Moericke, A., ... & Valsecchi, M. G. (2016). Influence of cranial radiotherapy on outcome in children with acute lymphoblastic leukemia treated with contemporary therapy. *Journal of Clinical Oncology*, *34*(9), 919-926.
47. Dunsmore, K. P., Winter, S. S., Devidas, M., Wood, B. L., Esiashvili, N., Chen, Z., ... & Hunger, S. P. (2020). Children's Oncology Group AALL0434: a phase III randomized clinical trial testing nelarabine in newly diagnosed T-cell acute lymphoblastic leukemia. *Journal of Clinical Oncology*, *38*(28), 3282-3293.
48. Candoni, A., Lazzarotto, D., Ferrara, F., Curti, A., Lussana, F., Papayannidis, C., ... & Foà, R. (2020). Nelarabine as salvage therapy and bridge to allogeneic stem cell transplant in 118 adult patients with relapsed/refractory T-cell acute lymphoblastic leukemia/lymphoma. A CAMPUS ALL study. *American journal of hematology*, *95*(12), 1466-1472.
49. Cremer, A., Hanoun, M., Wäsch, R., Raffel, S., Wethmar, K., Viardot, A., ... & Goekbuget, N. (2024). Outcome of Patients with Hematologic or Molecular Relapsed/Refractory (R/R) Acute T-Lymphoblastic Leukemia-Data from the GMALL Study Group. *Blood*, *144*, 1436.
50. Peirs, S., Matthijssens, F., Goossens, S., Van de Walle, I., Ruggero, K., De Bock, C. E., ... & Van Vlierberghe, P. (2014). ABT-199 mediated inhibition of BCL-2 as a novel therapeutic strategy in T-cell acute lymphoblastic leukemia. *Blood, The Journal of the American Society of Hematology*, *124*(25), 3738-3747.
51. Hamilton, B. K., Rybicki, L., Abounader, D., Adekola, K., Advani, A., Aldoss, I., ... & Majhail, N. S. (2017). Allogeneic hematopoietic cell transplantation for adult T cell acute lymphoblastic leukemia. *Biology of Blood and Marrow Transplantation*, *23*(7), 1117-1121.
52. Liu, Y., Easton, J., Shao, Y., Maciaszek, J., Wang, Z., Wilkinson, M. R., ... & Mullighan, C. G. (2017). The genomic landscape of pediatric and young adult T-lineage acute lymphoblastic leukemia. *Nature genetics*, *49*(8), 1211-1218.
53. Meyer, L. K., Huang, B. J., Delgado-Martin, C., Roy, R. P., Hechmer, A., Wandler, A. M., ... & Hermiston, M. L. (2020). Glucocorticoids paradoxically facilitate steroid resistance in T cell acute lymphoblastic leukemias and thymocytes. *The Journal of clinical investigation*, *130*(2), 863-876.
54. Meyers, R. M., Bryan, J. G., McFarland, J. M., Weir, B. A., Sizemore, A. E., Xu, H., ... & Tsherniak, A. (2017). Computational correction of copy number effect improves specificity of CRISPR–Cas9 essentiality screens in cancer cells. *Nature genetics*, *49*(12), 1779-1784.
55. Xu, J., Chen, C., Sussman, J. H., Yoshimura, S., Vincent, T., Pölönen, P., ... & Teachey, D. T. (2025). A multiomic atlas identifies a treatment-resistant, bone marrow progenitor-like cell population in T cell acute lymphoblastic leukemia. *Nature cancer*, *6*(1), 102-122
56. Canté-Barrett, K., Mendes, R. D., Li, Y., Vroegindeweij, E., Pike-Overzet, K., Wabeke, T., ... & Meijerink, J. P. (2017). Loss of CD44dim expression from early progenitor cells marks T-cell lineage commitment in the human thymus. *Frontiers in immunology*, *8*, 32.
57. Vester, S. K., Beavil, R. L., Lynham, S., Beavil, A. J., Graham, D. S. C., McDonnell, J. M., & Vyse, T. J. (2021). Nucleolin acts as the receptor for C1QTNF4 and supports C1QTNF4-mediated innate immunity modulation. *Journal of Biological Chemistry*, *296*.
58. Tari, K., Nasimian, A., Kazi, J. U., & Abroun, S. (2023). Venetoclax drug increases the apoptosis of T and B acute lymphoblastic leukemia cells by reducing the expression of BCL-2. *International Journal of Molecular and Cellular Medicine*, *12*(3), 229.
59. Lu, Y., Yang, X., Liu, L., Sun, X., Li, X., Zhao, P., ... & Dai, Y. (2025). Decoding the diagnostic biomarkers of mitochondrial dysfunction related gene variants in pediatric T cell acute lymphoblastic leukemia. *Scientific Reports*, *15*(1), 21144.

60. Lonetti, A., Cappellini, A., Bertaina, A., Locatelli, F., Pession, A., Buontempo, F., ... & Chiarini, F. (2016). Improving nelarabine efficacy in T cell acute lymphoblastic leukemia by targeting aberrant PI3K/AKT/mTOR signaling pathway. *Journal of hematology & oncology*, *9*(1), 114.
61. Xia, J., Sun, S., Jotte, M. R., Uy, G. L., Bohana-Kashtan, O., Sorani, E., ... & Link, D. C. (2019). CXCR4 Blockade By BL-8040 in T Cell Acute Lymphoblastic Leukemia Decreases Mitochondrial Mass and Induces Non-Apoptotic Cell Death. *Blood*, *134*, 2745.
62. Lock, R. B., Toscan, C. E., McCalmont, H., Evans, K., Doculara, L., Kosasih, H. J., ... & Smaill, J. B. (2023). The AKR1C3-Activated Prodrug, Achm-025, Eradicates Disease in Preclinical Models of Aggressive T-Cell Acute Lymphoblastic Leukemia.
63. Yamauchi, T., Uzui, K., Nishi, R., Shigemi, H., & Ueda, T. (2014). Reduced drug incorporation into DNA and antiapoptosis as the crucial mechanisms of resistance in a novel nelarabine-resistant cell line. *BMC cancer*, *14*(1), 547.
64. Dunsmore, K. P., Winter, S. S., Devidas, M., Wood, B. L., Esiashvili, N., Chen, Z., ... & Hunger, S. P. (2020). Children's Oncology Group AALL0434: a phase III randomized clinical trial testing nelarabine in newly diagnosed T-cell acute lymphoblastic leukemia. *Journal of Clinical Oncology*, *38*(28), 3282-3293.
65. Gossai, N. P., Devidas, M., Chen, Z., Wood, B. L., Zweidler-McKay, P. A., Rabin, K. R., ... & Teachey, D. T. (2023). Central nervous system status is prognostic in T-cell acute lymphoblastic leukemia: a Children's Oncology Group report. *Blood*, *141*(15), 1802-1811.
66. Dunsmore, K. P., Winter, S. S., Devidas, M., Wood, B. L., Esiashvili, N., Chen, Z., ... & Hunger, S. P. (2020). Children's Oncology Group AALL0434: a phase III randomized clinical trial testing nelarabine in newly diagnosed T-cell acute lymphoblastic leukemia. *Journal of Clinical Oncology*, *38*(28), 3282-3293.
67. Gossai, N. P., Devidas, M., Chen, Z., Wood, B. L., Zweidler-McKay, P. A., Rabin, K. R., ... & Teachey, D. T. (2023). Central nervous system status is prognostic in T-cell acute lymphoblastic leukemia: a Children's Oncology Group report. *Blood*, *141*(15), 1802-1811.