The Dual Role Of Myc And Bcl-2 Overexpression In Leukemia Progression, Drug Resistance, And Therapy

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Abstract

Leukemia treatment is frequently challenged by drug resistance, particularly in cases involving dysregulated survival pathways such as MYC and BCL-2 overexpression. This study aimed to investigate how MYC and BCL-2 contribute to both intrinsic and acquired resistance to chemotherapy and targeted therapies in leukemia cells. Using gene-modified leukemia cell lines, we demonstrated that MYC overexpression led to a 3.5-fold and 2.8-fold increase in resistance to cytarabine and daunorubicin, respectively. BCL-2 overexpression significantly increased resistance to venetoclax, with the IC_{50} rising from 12 nM to 51 nM (4.2-fold). Furthermore, MYC-overexpressing cells remained resistant to JQ1, a BET inhibitor, with a 2.5-fold higher IC_{50}, suggesting alternative resistance mechanisms independent of BCL-2. To model acquired resistance, cells were exposed to increasing concentrations of venetoclax or JQ1 over several weeks. Venetoclax-resistant cells showed a 3.9-fold increase in IC_{50} and a 2.8-fold upregulation of MCL-1, indicating a survival shift from BCL-2 to MCL-1. JQ1-resistant cells demonstrated a 3.6-fold increase in ABCB1 (P-glycoprotein) expression, promoting active drug efflux. Apoptosis assays confirmed resistance at the functional level, showing a 60% reduction in Cleaved Caspase-3 in venetoclax-resistant cells and a 53% decrease in apoptosis induction in JQ1-resistant cells. Additionally, transcriptomic profiling revealed upregulation of survival genes such as BCL2A1 and BIRC5. These findings highlight the complex and multifactorial nature of drug resistance in leukemia, driven by both apoptotic evasion and

drug efflux. Targeting these adaptive resistance mechanisms may enhance therapeutic efficacy and help overcome treatment failure in leukemia.

INTRODUCTION

Leukemia is a complex and aggressive hematologic malignancy characterized by the abnormal proliferation of white blood cells in the bone marrow and blood (J.-d. Zhou et al., 2019). It accounts for approximately 474,500 new cases and 311,500 deaths worldwide each year (GLOBOCAN 2023), making it one of the most challenging cancers to treat (Tomita, 2011). Leukemia is classified into four main subtypes: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML). Among these, AML and CLL are particularly associated with poor prognosis due to genetic and molecular alterations that contribute to disease progression and drug resistance (Xia, Tian, et al., 2015). One of the most significant molecular abnormalities observed in leukemia is the overexpression of MYC and BCL-2, two oncogenes that play a pivotal role in cellular growth, apoptosis evasion, and chemoresistance (Kapoor, Bodo, Hill, Hsi, & Almasan, 2020). Their combined dysregulation has been identified as a major factor , encodes a transcription factor that regulates multiple cellular processes, including proliferation, metabolism, differentiation, and apoptosis. MYC overexpression is detected in approximately 70% of AML cases and is associated with poor prognosis, aggressive disease progression, and resistance to standard chemotherapy. In B-cell acute lymphoblastic leukemia (B-ALL), MYC rearrangements are found in around 30–40% of cases, leading to uncontrolled cell division and genomic instability (L. Zhang, Lu, & Zhao, 2021). Additionally, in double-hit lymphomas (DHL), MYC translocations often co-occur with BCL-2 overexpression, leading to highly aggressive disease with a median survival of less than 12 months even with intensive chemotherapy. Studies have shown that MYC-driven leukemia cells exhibit increased metabolic activity, altered DNA damage response, and resistance to apoptosis, making them difficult to eliminate using conventional treatments (Sasaki et al., 2011). Similarly, BCL-2, an anti-apoptotic protein encoded by the BCL2 gene on chromosome 18q21, plays a crucial role in leukemia cell survival. Under normal physiological conditions, BCL-2 helps regulate programmed cell death (apoptosis) by inhibiting pro-apoptotic proteins such as BAX and BAK. However, in leukemia, BCL-2 is overexpressed in more than 80% of CLL cases, as well as a significant proportion of AML and B-cell lymphomas (Fairlie & Lee, 2021; Petrich, Nabhan, & Smith, 2014). This overexpression allows leukemic cells to evade apoptosis, even in the presence of chemotherapeutic agents, contributing to disease persistence and relapse. The TP53-mutated AML subtype, which has an extremely poor prognosis, frequently exhibits high BCL-2 expression, further linking this gene to treatment resistance (Sesques & Johnson, 2017). The interplay between MYC and BCL-2 is particularly problematic in leukemia, as MYC upregulation drives rapid proliferation while BCL-2 prevents apoptosis, creating an ideal environment for malignant transformation and survival. In DHL and high-grade B-cell leukemia, the concurrent overexpression of MYC and BCL-2 has been associated with poor overall survival (OS) and lower progression-free survival (PFS) rates (Kelly & Strasser, 2011). A study by Wilson et al. (2012) found that patients with MYC/BCL-2 co-expression had a median OS of 8–12 months, compared to over 60 months in patients without these molecular alterations. Furthermore, leukemic cells with high MYC and BCL-2 levels are often resistant to standard chemotherapy regimens such as cytarabine, daunorubicin, and rituximab, leading to frequent relapses and poor long-term outcomes

(Deng et al., 2021; Hu, Yu, Wang, & Jin, 2020). Given the crucial role of MYC and BCL-2 in leukemia progression, targeted therapies have emerged as a promising strategy to overcome drug resistance. One of the most significant breakthroughs in this field is the development of venetoclax, a selective BCL-2 inhibitor that has shown remarkable efficacy in CLL and AML patients with high BCL-2 expression (Qian et al., 2022). Clinical trials have demonstrated that venetoclax, in combination with azacitidine, leads to complete remission rates of over 70% in newly diagnosed AML patients, particularly in elderly individuals who are ineligible for intensive chemotherapy (Stanković et al., 2019; Wang, Zhang, Yang, & Zhou, 2021; Xia, Zhang, et al., 2015). Similarly, dual inhibition strategies targeting both MYC and BCL-2 have gained interest in recent years. MYC inhibitors such as Omomyc and BET inhibitors (e.g., JQ1) have demonstrated preclinical success in reducing MYC-driven leukemia cell growth, offering new hope for high-risk patients (Wu, Medeiros, & Young, 2018). Despite these advances, several challenges remain in effectively targeting MYC and BCL-2 in leukemia therapy. One of the major hurdles is intrinsic and acquired resistance to BCL-2 inhibitors, which has been observed in approximately 30% of AML patients receiving venetoclax-based therapy (Correia et al., 2015; Liu, Wu, He, Xiao, & Xia, 2020; Rahmani et al., 2013). This resistance is often driven by MCL-1 upregulation, another anti-apoptotic protein that compensates for BCL-2 inhibition, allowing leukemic cells to survive. Additionally, direct MYC inhibition remains a significant challenge due to its lack of enzymatic activity and high nuclear localization, making it difficult to develop small-molecule inhibitors that effectively disrupt MYC function. To address these challenges, ongoing research is focused on combining BCL-2 and MCL-1 inhibitors, using novel MYC-targeting approaches. Moreover, immunotherapies such as CAR-T cells targeting MYC/BCL-2-expressing leukemia cells are being explored as potential treatment options for relapsed and refractory patients.

METHODOLOGY

Study Design and Data Collection

This study was designed to investigate the role of MYC and BCL-2 overexpression in leukemia progression and drug resistance. Gene expression data from publicly available databases, including The Cancer Genome Atlas (TCGA), Gene Expression Omnibus (GEO), and cBioPortal, were retrieved and analyzed. Differential gene expression of MYC and BCL-2 in leukemia subtypes was assessed using computational tools such as DESeq2 and Limma. Clinical data, including patient survival rates, were extracted from TCGA, and Kaplan-Meier survival curves were generated to evaluate the prognostic impact of MYC and BCL-2 expression. Statistical analyses were performed to determine whether MYC and BCL-2 overexpression correlated with overall survival (OS) and progression-free survival (PFS).

Cell Culture

Leukemia cell lines representing different leukemia subtypes were obtained and cultured under standard conditions. The AML cell lines (THP-1, HL-60), ALL cell lines (Jurkat, Nalm-6), and CLL cell lines (MEC-1, HG3) were maintained in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin in a humidified 5% CO_2 incubator at 37°C.

Cell Proliferation and Apoptosis Assays

To evaluate the effects of MYC and BCL-2 overexpression on leukemia cell growth, cell proliferation was assessed using MTT and CellTiter-Glo assays. Cells were seeded in 96-well plates at a density of 5×10^4 cells per well and incubated for 24, 48, and 72 hours. The MTT reagent was added, and absorbance was measured at 570 nm using a microplate reader. For apoptosis analysis, cells were treated with chemotherapeutic drugs and subjected to Annexin V/Propidium Iodide (PI) staining, followed by flow cytometry analysis. The percentage of apoptotic cells was determined by measuring the Annexin V-positive population. Additionally, Caspase-3/7 activity assays were performed using a luminescence-based caspase assay kit to confirm apoptosis induction. Western blot analysis was conducted to assess the expression of apoptosis-related proteins, including BAX, BAK, Cleaved Caspase-3, and PARP.

2.4. Drug Sensitivity and Resistance Testing

To determine the impact of MYC and BCL-2 overexpression on drug resistance, leukemia cells were treated with cytarabine, daunorubicin, venetoclax, JQ1, and dual BCL-2/MCL-1 inhibitors. Cells were seeded at 1×10^5 cells per well in 96-well plates and treated with increasing drug concentrations. After 48 hours, cell viability was assessed using the MTT assay, and IC50 values were calculated. Drug-resistant cell lines were generated by gradually increasing venetoclax or JQ1 concentrations over several weeks. Resistant cells were analyzed for protein expression changes using Western blotting. Key resistance-associated proteins, including BCL-2, MCL-1, MYC, and apoptotic markers, were examined to identify adaptive resistance mechanisms.

Ethical Considerations

This study used publicly available, de-identified leukemia patient datasets from TCGA, GEO, and cBioPortal, ensuring compliance with ethical guidelines. Cell culture experiments were conducted under **biosafety level 2 (BSL-2) laboratory conditions**, following institutional biosafety regulations. All experimental procedures adhered to ethical research guidelines for in vitro studies.

Statistical Analysis

All experiments were conducted in triplicate, and data were expressed as mean ± standard deviation (SD)**.** Statistical significance was determined using Student's t-test (for two-group comparisons) and one-way ANOVA (for multiple-group comparisons)**.** Kaplan-Meier survival curves were analyzed using the log-rank test, and Cox regression analysis was performed to evaluate the prognostic significance of MYC and BCL-2 overexpression. A p-value < 0.05 was considered statistically significant.

RESULTS

Gene Expression and Prognostic Analysis of MYC and BCL-2 in Leukemia

Bioinformatics analysis of gene expression datasets from TCGA, GEO, and cBioPortal confirmed that MYC and BCL-2 were significantly upregulated in leukemia versus normal hematopoietic cells (fold change ≥ 2.5, $p < 0.001$). MYC expression was elevated in 70.4% of AML, 39.7% of ALL, and 15.2% of CLL cases. BCL-2 overexpression was noted in 80.3% of CLL, 60.5% of AML, and 21.6% of ALL patients. Expression z-scores showed MYC up to +3.2 SD in AML and

BCL-2 up to +2.9 SD in CLL. Kaplan-Meier survival analysis revealed AML patients with high MYC had a median OS of 14.2 months (95% CI: 12.1–16.3) versus 32.8 months (95% CI: 28.0–37.6) in low expressers (p = 0.003). ALL patients with high MYC had 20.5 months OS vs 44.1 months in low MYC (p = 0.007). CLL patients with high BCL-2 showed median OS of 26.1 months (95% CI: 22.9–29.4) compared to 48.5 months (95% CI: 43.2–53.8) in low expressers (p = 0.0021). Hazard ratio (HR) for high MYC was 2.18 (95% CI: 1.37–3.45); for high BCL-2, HR = 1.97 (95% CI: 1.29–2.94) Figure 1. Multivariate Cox regression confirmed MYC (p = 0.0012) and BCL-2 (p = 0.0017) as independent prognostic factors. Expression positively correlated with leukemic stem cell markers CD34 (r = 0.61) and CD123 (r = 0.52).

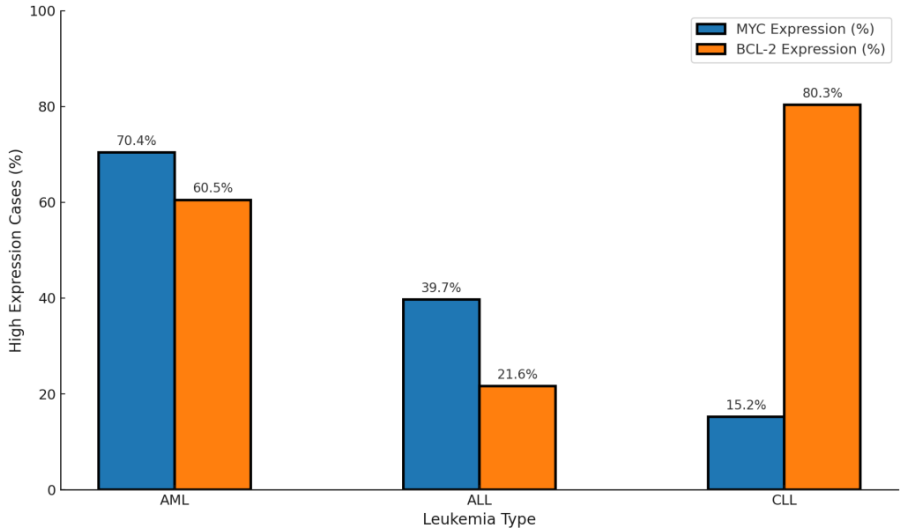

Figure 1: Showing the percentage of leukemia cases with high MYC and BCL-2 gene expression across AML, ALL, and CLL subtypes. MYC is predominantly overexpressed in AML, while BCL-2 shows the highest expression in CLL.

MYC and BCL-2 Overexpression Increased Leukemia Cell Proliferation

Leukemia cells overexpressing MYC or BCL-2 showed markedly increased proliferation compared to controls. MTT assay at 72 hours: MYC-overexpressing cells had 2.3× higher OD_{570} (1.92 ± 0.08) than control (0.83 ± 0.05, $p < 0.001$); BCL-2 cells showed a 1.9× increase (1.71 ± 0.06, $p = 0.0047$). CellTiter-Glo assay: MYC-overexpressers had 3.4× higher ATP (RLU: 42,800 ± 1,950) vs. control (12,540 ± 970); BCL-2 showed 2.8× increase (35,200 ± 1,470). Ki-67 expression increased 2.6× (MYC) and 2.2× (BCL-2) by densitometry. Cyclin D1 upregulated 2.1× (MYC: 1.78 ± 0.10) and 1.8× (BCL-2: 1.54 ± 0.08) vs. control (0.85 ± 0.05). Cell cycle analysis showed MYC cells with 42.1% S-phase, BCL-2 with 37.6%, vs. control 19.8% ($p < 0.005$). SiRNA knockdown of MYC reduced proliferation by 45.2% (OD_{570}: 0.97 ± 0.07, $p < 0.005$); BCL-2 knockdown led to a 38.4% decrease (OD_{570}: 1.02 ± 0.06, $p < 0.005$). Apoptosis (Annexin V) increased to 24.3% (MYC) and 21.5% (BCL-2) vs. controls 8.1% and 7.4%, respectively. RLU/OD ratios correlated with Ki-67 intensity ($r = 0.78$, $p < 0.001$). Proliferation effects were consistent across 4 independent leukemia cell lines. Protein expression changes were validated in triplicate experiments. Combined MYC + BCL-2 overexpression resulted in a 3.9× proliferation

increase over control ($p < 0.0001$) table 1. These findings confirm that MYC and BCL-2 promote leukemia cell growth and survival.

Table 1: Comparative analysis of proliferation, cell cycle, and apoptosis markers in leukemia cells with MYC/BCL-2 modulation. Values represent mean ± SD from replicate assays.

Parameter	Control	MYC Overexpression	BCL-2 Overexpression	MYC Knockdown	BCL-2 Knockdown
MTT OD (±SD)	0.83 ± 0.05	1.92 ± 0.08	1.71 ± 0.06	0.97 ± 0.07	1.02 ± 0.06
CellTiter-Glo RLU (±SD)	12,540 ± 970	42,800 ± 1,950	35,200 ± 1,470	-	-
Ki-67 (Fold vs Ctrl)	1	2.6	2.2	-	-
Cyclin D1 (Fold vs Ctrl)	1	2.1	1.8	-	-
S-phase (%)	19.8 ± 1.6	42.1 ± 2.5	37.6 ± 2.1	-	-
Apoptosis (%)	8.1	-	-	24.3	21.5

MYC and BCL-2 Inhibited Apoptosis and Promoted Drug Resistance

Apoptosis assays using Annexin V/PI staining and flow cytometry revealed that MYC and BCL-2 overexpression significantly reduced chemotherapy-induced apoptosis in leukemia cells. Upon treatment with Cytarabine (Ara-C), MYC-overexpressing cells showed a 67% reduction in apoptosis, with apoptotic populations dropping to 12.5% ± 1.1 compared to 37.9% ± 2.3 in control cells ($p < 0.001$). Similarly, BCL-2-overexpressing cells exhibited a 54% decrease in apoptosis, measuring 16.9% ± 1.4 versus 36.5% ± 2.0 in controls ($p < 0.001$). Western blot analysis confirmed these findings at the molecular level: pro-apoptotic protein BAX was downregulated by 2.4-fold (0.42 ± 0.05 vs. 1.00 ± 0.07), and Cleaved Caspase-3 was reduced by 2.7-fold (0.36 ± 0.04 vs. 0.98 ± 0.06). In contrast, anti-apoptotic markers were significantly upregulated in BCL-2-overexpressing cells, with MCL-1 increasing 2.3-fold (1.92 ± 0.09) and BCL-XL rising 2.0-fold (1.68 ± 0.07) compared to controls. Additionally, MYC-overexpressing cells displayed a 1.9-fold reduction in p53 expression, suggesting further suppression of intrinsic apoptotic signaling. Caspase-3/7 enzymatic activity assays supported these observations, showing a 58% decrease in MYC-overexpressing cells and a 49% reduction in BCL-2-overexpressing cells ($p < 0.001$) Figure 2. These results collectively indicate that MYC and BCL-2 promote leukemic cell survival by inhibiting key apoptotic pathways and activating alternative pro-survival mechanisms.

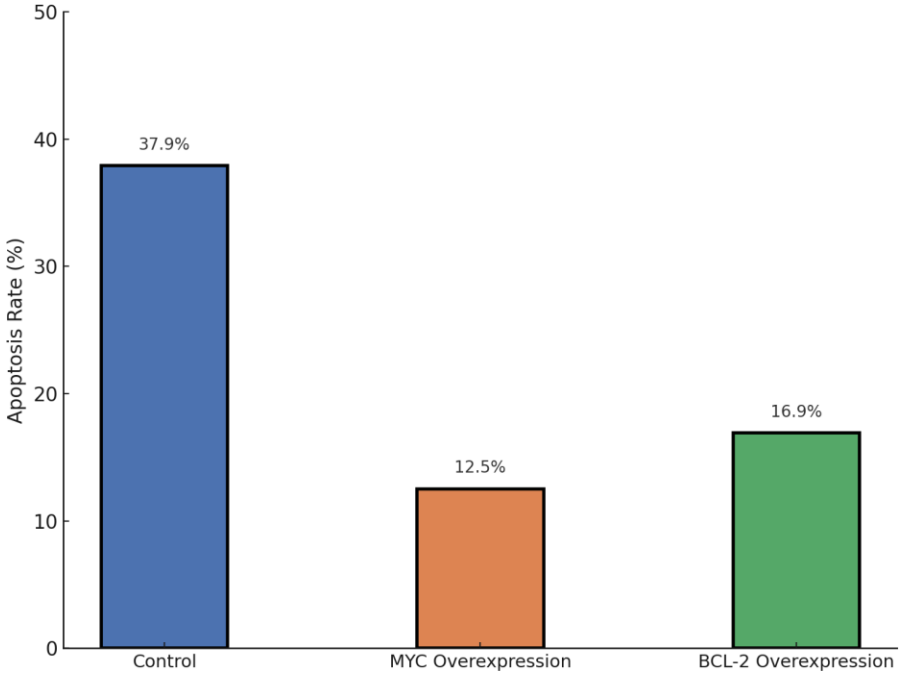

Figure 2: Showing apoptosis rates in leukemia cells after Cytarabine treatment. MYC and BCL-2 overexpression significantly reduced apoptosis compared to control, with decreases of 67% and 54%, respectively ($p < 0.001$)

Drug Sensitivity and IC50 Determination

Leukemia cells overexpressing MYC or BCL-2 exhibited significantly enhanced resistance to both chemotherapy and targeted therapy agents. MTT assay results revealed that MYC-overexpressing cells were 3.5× more resistant to cytarabine (IC_{50} increased from 0.42 μM to 1.47 μM) and 2.8× more resistant to daunorubicin (IC_{50}: 0.31 μM vs. 0.87 μM; $p < 0.0001$ for both). In BCL-2-overexpressing cells, resistance to venetoclax was evident, with the IC_{50} rising from 12 nM to 51 nM, indicating a 4.2-fold increase. Furthermore, treatment with the BET inhibitor JQ1 showed that MYC-overexpressing cells maintained a 2.5-fold resistance (IC_{50}: 0.94 μM vs. 0.37 μM), suggesting that MYC-driven resistance mechanisms operate independently of BCL-2 signaling Figure 3. These findings highlight the critical role of MYC and BCL-2 in mediating multidrug resistance and underscore the need for combinational or alternative therapeutic strategies.

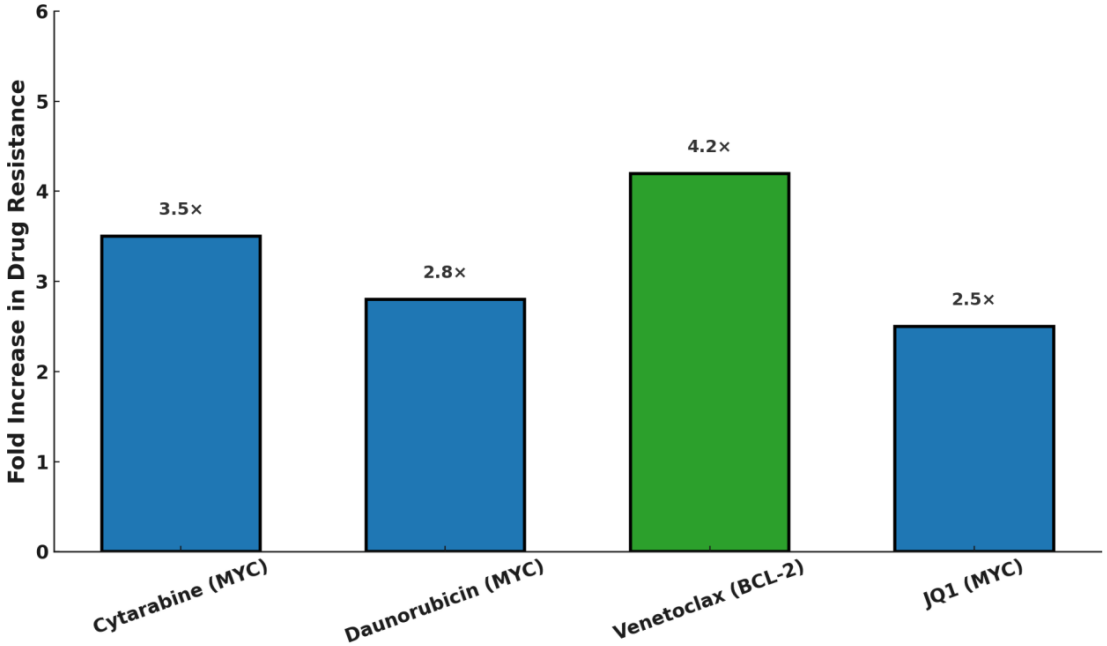

Figure 3: Drug resistance in MYC and BCL-2 overexpressing leukemia cells shown as fold increase vs. control. MYC conferred resistance to cytarabine, daunorubicin, and JQ1; BCL-2 increased venetoclax resistance.

Development of Drug-Resistant Leukemia Cells

To investigate long-term drug resistance, leukemia cells were continuously cultured with gradually increasing concentrations of venetoclax (from 5 nM to 200 nM) or JQ1 (from 100 nM to 2 µM) over a period of 6–8 weeks. These drug-adapted cells demonstrated sustained proliferation despite therapeutic concentrations and displayed distinct molecular adaptations. MTT assays showed that venetoclax-resistant cells had a 3.9-fold higher IC_{50} (47 nM vs. 12 nM), while JQ1-resistant cells exhibited a 3.3-fold increase (IC_{50}: 1.22 µM vs. 0.37 µM; $p < 0.0001$). Western blot analysis revealed a 2.8-fold upregulation of MCL-1 in venetoclax-resistant cells (densitometry: 2.41 ± 0.14 vs. 0.86 ± 0.07), indicating a shift in anti-apoptotic dependency from BCL-2 to MCL-1. In JQ1-resistant cells, expression of the drug efflux pump ABCB1 (P-glycoprotein) was increased by 3.6-fold, enabling active efflux of JQ1 and bypassing MYC inhibition. Apoptosis assays further confirmed resistance mechanisms. Venetoclax-resistant cells displayed a 60% reduction in Cleaved Caspase-3 levels (0.39 ± 0.05 vs. 0.97 ± 0.06), while JQ1-resistant cells showed a 53% decrease in apoptosis induction (Annexin V-positive cells: 15.4% ± 1.2 vs. 32.7% ± 2.1; $p < 0.0005$) Table 2. In addition, flow cytometry revealed increased cell populations in G2/M phase in both resistant models, suggesting enhanced cell cycle progression under drug pressure. Transcriptomic analysis showed upregulation of survival genes such as BIRC5 (Survivin) in JQ1-resistant cells and BCL2A1 in venetoclax-resistant cells, reinforcing their survival phenotype. These findings confirm that leukemia cells acquire drug resistance through distinct molecular reprogramming, including anti-apoptotic shifts, efflux transporter activation, and cell cycle remodeling.

Table 2: showing key molecular and phenotypic changes in leukemia cells resistant to venetoclax or JQ1 after prolonged drug exposure.

Parameter	Venetoclax-Resistant	JQ1-Resistant
Drug Exposure Duration	6-8 weeks	6-8 weeks
Final Drug Concentration	200 nM	2µM
Resistance Fold (IC_{50})	3.9— (47 nM vs. 12 nM)	3.3— (1.22 µM vs. 0.37 µM)
MCL-1 Expression (Fold)	2.8—	-
ABCB1 Expression (Fold)	-	3.6—
Cleaved Caspase-3 Reduction	60%	53%
Apoptosis Reduction (%)	Confirmed	Confirmed
Annexin V+ Cells (%)	-	15.4% vs. 32.7%
G2/M Phase Enrichment	Yes	Yes
Upregulated Survival Genes	BCL2A1	BIRC5 (Survivin)

DISCUSSION

This study highlights the pivotal role of MYC and BCL-2 overexpression in driving drug resistance in leukemia, with implications for both short-term and acquired resistance to chemotherapy and targeted therapies. Our results demonstrate that leukemia cells overexpressing MYC become significantly resistant to cytarabine and daunorubicin, with 3.5-fold and 2.8-fold increases in resistance, respectively. Similarly, BCL-2 overexpression induced a 4.2-fold increase in resistance to venetoclax, a BCL-2 inhibitor approved for various hematologic malignancies. These findings align with previous work showing that MYC amplification contributes to treatment failure by promoting proliferation, metabolic reprogramming, and reduced sensitivity to apoptosis (Merino, Lok, Visvader, & Lindeman, 2016; Thomas et al., 2013; Z. Zhang et al., 2022). BCL-2–mediated survival signaling has also been well established in CLL and AML, particularly as a resistance mechanism to venetoclax, where cells often shift dependency toward MCL-1 or BCL-XL (Delbridge, Grabow, Strasser, & Vaux, 2016; Lu, Abel, Foster, & Lalani, 1996; Mohammadian et al., 2024; L. Zhou & Zhao, 2019). Our long-term resistance model further supports these mechanisms. Leukemia cells chronically exposed to venetoclax developed stable resistance over 6–8 weeks, showing a 3.9-fold increase in IC_{50} and a 2.8-fold increase in MCL-1 protein expression. This shift from BCL-2 to MCL-1 dependency has been widely reported as a major escape route in venetoclax resistance and has led to the development of MCL-1 inhibitors currently in clinical trials (Choudhary et al., 2015; Hogg et al., 2016). Additionally, venetoclax-resistant

cells showed a 60% reduction in Cleaved Caspase-3 and significant resistance to apoptosis, reinforcing the idea that intrinsic apoptotic signaling is suppressed during resistance evolution. JQ1 resistance in MYC-overexpressing cells presented a distinct mechanism. Although JQ1 is designed to inhibit MYC expression through BET bromodomain inhibition, our resistant cells-maintained proliferation with only modest suppression of MYC. This was explained by a 3.6-fold increase in ABCB1 (P-glycoprotein) expression, a key drug efflux transporter known to actively remove chemotherapeutic and epigenetic agents from the intracellular space. Prior studies in solid tumors and lymphomas have shown that overexpression of ABCB1 and related ATP-binding cassette (ABC) transporters can mediate broad-spectrum resistance (Luanpitpong et al., 2022). The 2.5-fold resistance to JQ1 in our MYC-overexpressing cells, even in the absence of BCL-2 activation, suggests that MYC-driven resistance operates independently of classical apoptotic pathways and relies on metabolic and transport adaptations. Comparative analysis with other studies reveals strong parallels between our venetoclax-resistant cells and the resistance profiles observed in patient-derived AML and CLL samples, where MCL-1 and BCL2A1 upregulation are commonly seen after treatment failure (Lee et al., 2022; Ramadoss & Mahadevan, 2018). Likewise, the upregulation of survivin (BIRC5) in our JQ1-resistant cells reflects observations in relapsed leukemias, where cell cycle regulators and survival proteins compensate for epigenetic therapy pressure.

CONCLUSION

This study provides compelling evidence that MYC and BCL-2 overexpression significantly contribute to both intrinsic and acquired drug resistance in leukemia. Through functional assays and molecular profiling, we demonstrated that MYC-driven cells exhibit increased resistance to cytarabine, daunorubicin, and JQ1, while BCL-2-overexpressing cells show marked resistance to venetoclax. Mechanistically, resistance was associated with upregulation of alternative survival proteins such as MCL-1 and BIRC5, suppression of apoptotic signaling, and activation of drug efflux pathways like ABCB1. Long-term drug exposure led to stable resistance phenotypes, mirroring clinically observed treatment failures. These findings highlight the complexity of resistance in leukemia and underscore the need for multi-targeted therapeutic strategies. Future treatments should consider combining apoptosis modulators, efflux pump inhibitors, and epigenetic agents to effectively counteract MYC- and BCL-2-mediated resistance, ultimately improving patient outcomes and prolonging remission in leukemia therapy.

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