Can BATF Expression Serve as a Predictive Marker for Treatment Necessity in Chronic Lymphocytic Leukemia?

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is the most common leukemia in Western countries. The clinical outcome of CLL is heterogeneous and is affected by immunogenic properties. The basic leucine zipper transcription factor (BATF) is a key regulator of Th17 and TFH cells, and plays an important role in B cell activation. The role of BATF in CLL pathogenesis remains unclear. This study aimed to evaluate BATF mRNA expression in whole blood and intracellular BATF levels in different lymphocyte subsets of CLL patients and to investigate their potential association with clinical outcomes. Long-term clinical follow-up data were used to compare BATF levels between patients who required treatment and those managed without therapy. *BATF* mRNA expression in whole blood was significantly higher in patients than in healthy subjects. Similarly, elevated BATF levels were found in $CD19^+$ B, $CD3^+$ T, $CD3^+CD4^+$ T helper, $CD8^+$ T, and TFH cells of CLL patients by flow cytometry. A positive correlation was observed between BATF levels and the count of $CD5^+CD19^+$ B-CLL cells. Notably, BATF levels in lymphocytes, $CD4^+$T, $CD8^+$ T and TFH cells were lower in CLL patients who required treatment than the levels in patients who required no treatment. Elevated BATF expression in CLL patients suggests its potential role in CLL pathogenesis. Reduced levels of BATF in $CD8^+$ T cells in patients who required treatment may indicate a reduced cytotoxic response against malignant cells. These findings might indicate that BATF expression could serve as a potential biomarker for predicting disease progression and treatment necessity in CLL.

Keywords: BATF, Basic leucine zipper transcription factor, T follicular cell, CLL, Chronic lymphocytic leukemia

INTRODUCTION

Chronic lymphocytic leukemia (CLL) which is the most common leukemia in the elderly is characterized by the accumulation of $CD19^+$ cells expressing CD5 in peripheral blood, bone marrow and lymph nodes.[1,2] The clinical outcome of CLL is highly heterogeneous, ranging from indolent forms that require no therapy to aggressive disease with rapid progression.[2] The genomic, epigenetic, and immunogenetic properties affect the clinical outcome of CLL.[3] Immunoglobulin heavy chain (IgVH) mutation, CD38 positivity, mutation of TP53, the presence of chromosomal deletions in 17p and 11q, and increased activation-induced cytidine deaminase (AID) mRNA level are associated with disease progression, however, the molecular pathogenesis of the disease has not yet been elucidated.[4-6] In addition to these genetic alterations, recent data showed that immune dysregulation contributes significantly to CLL progression. In particular, follicular helper T cells (TFH) and Th17 cells were increased in CLL patients and correlated with some prognostic markers.[7,8]

Basic leucine zipper transcription factor (BATF) is encoded by the BATF gene on chromosome 14,[9] and is a key regulator of TFH and Th17 cell differentiation and function.[10,11]

Studies in BATF-knockout mice have shown the absence of Th17 cells and reduced plasma interleukin (IL)-17 levels, underscoring its critical role in immune cell development.[12] BATF expression is induced by IL-4 and IL-6, and it plays a critical role in B cell expansion, AID regulation, and isotype switching in B cells.[13,14] In addition to its well established functions in Th17 and TFH cells differentiation, BATF also contributes to the maintenance of regulatory T cells (Treg) identity, thereby playing a role in the regulation of immune homeostasis and tolerance.[15] Aberrant BATF expression is thought to have a role in the pathogenesis of autoimmune and malignant diseases, highlighting the critical function of BATF as a molecular regulator that modulates the balance between immune activation and tolerance.[16,17] Recent studies have indicated that BATF plays a significant role in the pathogenesis of hematologic malignancies.[18] Aberrant BATF expression has been reported to contribute to the uncontrolled proliferation and survival of malignant cells in diffuse large B-cell lymphoma (DLBCL) and acute myeloid leukemia (AML).[19,20] These findings suggest that dysregulated BATF activity may serve both as a biomarker and as a potential therapeutic target in hematologic cancers. Our previous studies demonstrated elevated AID expression in CLL patients, which correlated with chromosomal deletions.[21,22] Additionally, we observed increased $CD8^+$ T and TFH cells, alongside a decrease in $CD4^+$ T cells. In line with these findings, recent studies reported that AID, TFH and Th17 cells have increased in CLL patients.[23-25] These observations suggest that BATF, as a common upstream regulator of these immune processes, may play an important role in CLL pathogenesis. However, the role of BATF in CLL pathogenesis has not been elucidated. In this study, BATF mRNA expression in whole blood and intracellular BATF levels in T, B, and TFH cells were evaluated in CLL patients.[26] In addition, we analyzed the long-term clinical follow-up data to assess the potential impact of BATF levels in patients who required treatment versus those under follow-up without treatment. By elucidating the role of BATF in CLL, this study may provide new insights into disease progression and potential biomarkers for predicting treatment necessity.

MATERIALS AND METHODS

Study Population

Peripheral blood samples were collected from 34 CLL patients and 15 healthy subjects between October 2015 and February 2016. The CLL patient group included 24 males (70.6 %) and 10 females (29.4%), with a median age of 62 (range, 51-84 years) years. The control group consisted of 10 males and 5 females with a median age of 58 (range, 53-68 years) years. All subjects underwent a complete physical examination, no symptoms of acute or chronic infection were detected. All patients met the CLL/IW 2008 diagnostic criteria and showed the characteristic $CD5^+CD19^+$ immunophenotypic profile. According to the Binet stage classification, 44% of patients were classified as Binet A (n= 15), 29% as Binet B (n= 10), and 27% as Binet C (n= 9). According to the Rai stage classification, 12% of patients were in Rai stage 0 (n= 4), 42% in Rai stage 1 (n= 14), 29% in Rai stage 2 (n= 10), 12% in Rai stage 3 (n= 4), and 5% in Rai stage 4 (n= 2). The clinical and cytogenetic features of the patients are summarized in Table 1.

At the time of blood sampling, none of the patients were receiving treatment or taking any medication. None of the patients or healthy controls had any non-infectious comorbidities at the time of enrollment. Patients were clinically followed up until October 2024. During the follow-up period, 19 patients required treatment at different time points, while the remaining 15 patients remained untreated. The median starting time of treatment was 17 months (min-max; 1-69 months) (Table 2). The written informed consent was obtained according to the Helsinki Declaration, and the study was approved by the local ethics committee (Istanbul University, Istanbul Medical Faculty Ethics Committee).

RNA Extraction and cDNA Preparation for Analysis of BATF mRNA Expression

Total RNA was isolated from whole blood using a QiaAmp RNA Blood Mini Kit (Qiagen, USA). RNA quality and quantity were checked using a NanoDrop 2000c (Thermo Fisher Scientific, Waltham, MA, USA). Samples that did not meet the quality or quantity criteria were re-isolated.

Table 1. Clinical and cytogenetic features of the patients

		CLL	Healthy Control
n		34	15
Sex	Male (n)	24	10
	Female (n)	10	5
Mean Age, years (min - max)	62 (51 - 84)	58 (53 - 68)	
WBC (10^6/ml), mean (min - max)	78.2 (5.2 - 226.3)		
$CD5^+CD19^+$ (%), mean (min - max)	66.9 (32.7 - 95.5)		
Binet Stage (n)	A	15	-
	B	10	-
	C	9	-
Rai Stage (n)	0	4	-
	1	14	-
	2	10	-
	3	4	-
	4	2	-
FISH Abnormalities (n)	del13q14	5	-
	del11q22.3	3	-
	del17p13	1	-
	Normal	19	-
	Not Performed	6	-
CD38 Status (n) 30 %< CD38 Negative 30% ≥ CD38 Positive			
	Negative	20	-
	Positive	11	-
	Not Performed	3	-
Infection	No	No	
Treatment	No Treatment	34	-

For cDNA synthesis, 1 μg of total RNA, hexamers (Roche Diagnostics, Mannheim, Germany), and Moloney murine leukemia virus reverse transcriptase (Thermo Fisher Scientific, Waltham, MA, USA) were used in accordance with the manufacturer's protocol.

BATF mRNA expressions beside a reference gene (hypoxanthine phosphoribosyltransferase 1 [HPRT1]) using real-time quantitative reverse transcription polymerase chain reaction (PCR) on a Light Cycler 480 II Instrument, with the Real-Time Ready Universal Probe Library Assay were analyzed (Roche Diagnostics, Mannheim, Germany). PCR conditions were as follows: Initial denaturation at 95^{0}C for 10 min, and then 45 cycles of denaturation for 10 seconds (s) at 95^{0}C, annealing for 30 s at 60^{0}C, and extension for 1 s at 72^{0}C. Each sample was studied in duplicate. Relative expressions were calculated in accordance with the $2^{-\Delta\Delta Ct}$ method, based on the mathematical model of Livak et al.[27] Primer sequences were 5′-GTTCTGTTTCTCCAGGTCC-3′ (forward) and 5′-GAAGAATCGCATCGCTGC-3′ (reverse) for BATF, 5'-GACCAGTCAACAGGGGACAT-3' (forward) and 5'-GTGTCAATTATATCTTCCACAATCAAG-3' (reverse) for HPRT1.

The Flow Cytometric Analyses of Lymphocyte Subsets and Intracellular BATF Levels

The intracellular BATF levels in T and B lymphocyte subsets were analyzed using the whole blood lysis method with two distinct flow cytometry panels. Freshly drawn peripheral whole blood samples of 100 μL were labeled with anti-human CD5-PE-Cy7 (clone L17F12) and anti-human CD19-APC (clone SJ25C1) for B cell panel or were labeled as anti-human CD3-PE-Cy7 (clone UCTH1), anti-human CD4-APC (clone RPA-T4) and anti-human C-X-C chemokine receptor type 5 (CXCR5)-FITC (clone J252D4) monoclonal antibodies (mAbs)

Table 2. The treatment status of patients who were followed up between 2015-2024

Patient		n
Patients who required no treatment		15
Patients who required treatment		19
First Line	Ibrutinib	2
	Endoxan	10
	Venetoclax	-
	R-Benda	1
	Rituximab alone	-
	R-CHOP	1
	Venetoclax	-
	Endoxan + Cyclophosphamide	4
	FCR	1
Second Line	Ibrutinib	4
	Endoxan	-
	Venetoclax	1
	R-Benda	2
	Rituximab alone	1
	R-CHOP	-
	Venetoclax	5
	Endoxan + Cyclophosphamide	-
	FCR	1
Third and Later Line	Ibrutinib	4
	Endoxan	-
	Venetoclax	-
	R-Benda	1
	Rituximab alone	-
	R-CHOP	-
	Venetoclax	1
	Endoxan + Cyclophosphamide	-
	FCR	-

for T cell panel. All mAbs were purchased from Biolegend (San Jose, CA, USA). After lysing process of the erythrocytes, cells were washed with phosphate-buffered saline (PBS), fixated, and permeabilized using paraformaldehyde/saponin solution (Cytofix&Cytoperm Kit, Biolegend, San Jose, CA), and finally stained with PE-conjugated-BATF (clone 9B5A13) mAbs for 20 min at room temperature and analyzed using FACSCalibur system (BD Bioscience, USA). All mAbs were purchased from Biolegend (San Jose, CA, USA). The data were collected on a FACSCalibur system

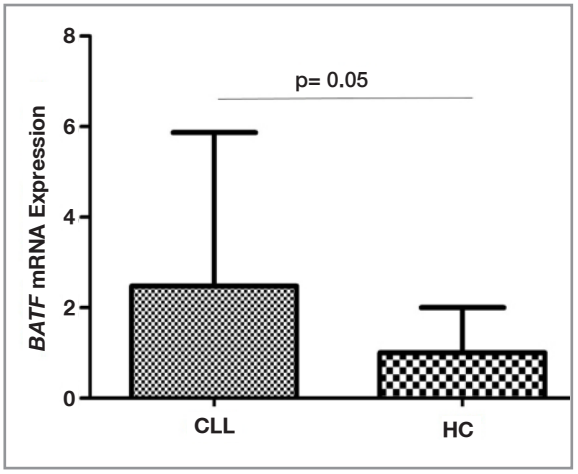

Figure 1. BATF mRNA expression in CLL patients and healthy subjects

(BD Biosciences, USA) and analyzed using the CellQuest Pro operating system software (BD Biosciences, USA).

Ethical Approval: This sttudy is approved by the Istanbul University, Istanbul Medical Faculty Ethics Committee; May 02, 2025, No: 09).

Statistical Analysis

The normality of data distribution was assessed using the Shapiro-Wilk test. The Student's t-test was used in the statistical analysis of the independent and paired groups showing normal distribution. Nonparametric variables were performed using the Mann-Whitney U test to analyze associations in quantitative data. P values less than 0.05 were considered statistically significant. Pearson's correlation test was used for correlation analysis. All statistical analyses were performed using GraphPAD Instat version 5.03 (GraphPad Software Inc., San Diego, CA, USA).

RESULTS

BATF mRNA Expression in Whole Blood of CLL Patients

BATF mRNA expression in whole blood was compared between CLL patients and healthy subjects. The results demonstrated a significant increase in BATF mRNA expression in whole blood of CLL patients compared to healthy subjects (p= 0.05)

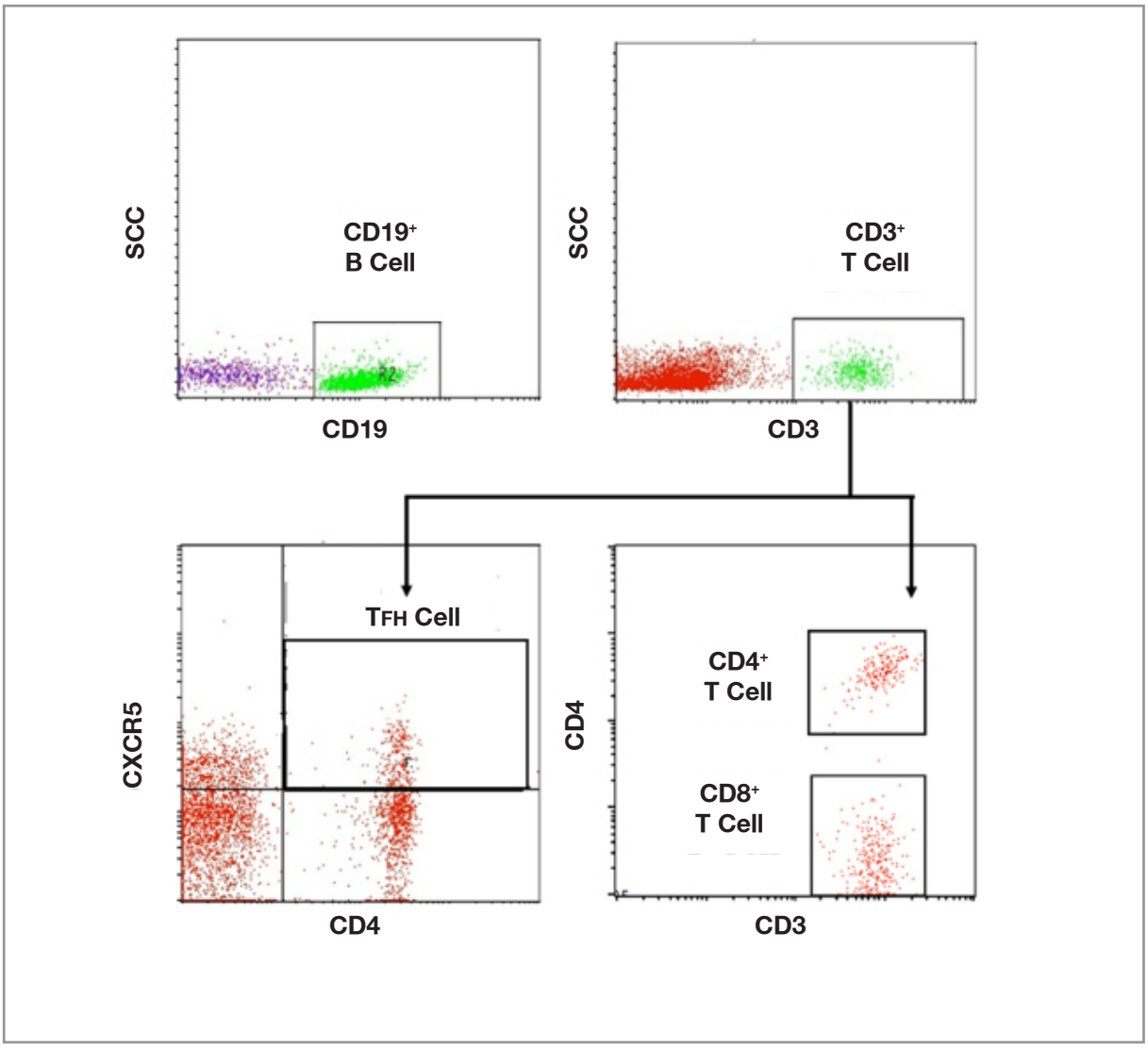

Figure 2. Peripheral blood samples were stained with anti-CD5, -CD3, -CD19, and -BATF mAbs. Representative dot-plot analyses illustrate BATF levels in lymphocytes, $CD19^+$ B cells, $CD3^+$ T cells, $CD3^+CD4^+$ T helper cells, $CD8^+$ T cells and TFH cells in CLL patients and healthy subjects.

(Figure 1). However, no significant difference in BATF expression were observed according to Rai or Binet clinical staging systems, CD38 positivity, or cytogenetic status among the patient groups (data not shown).

Intracellular BATF Levels in T Cell Subsets

Intracellular BATF levels in peripheral blood samples were analyzed using flow cytometry. Lymphocytes were gated based on their forward (FSC) and side scatter (SSC) characteristics. *BATF* levels were analyzed in various immune cell subsets, including lymphocytes, $CD19^+$ B, $CD3^+$ T cells, $CD3^+CD4^+$ T helper cells, $CD3^+CD4^-$ T cells ($CD8^+$ T cells), and $CD3^+CD4^+CXCR5^+$ TFH cells (Figure 2). The results showed significantly increased BATF levels in lymphocytes and $CD19^+$ B cells of CLL patients compared to healthy subjects ($p= 0.0013$ and $p= 0.0011$, respectively) (Figure 3). Similarly, *BATF* levels were elevated in $CD3^+$T, $CD3^+CD4^+$ Thelper, $CD8^+$ T cells, and TFH cells in CLL patients compared to healthy subjects ($p= 0.0032$, $p= 0.0154$, $p= 0.004$, and $p= 0.0005$, respectively) (Figure 3).

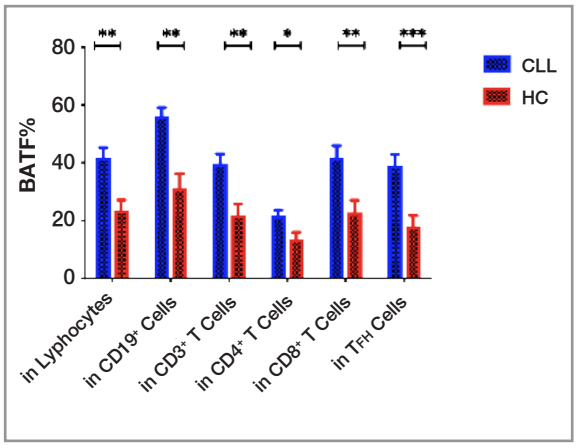

Figure 3. The statistical graphs represent the percentage of BATF level of CD19⁺ B cells, lymphocytes, CD3⁺ T cells, CD3⁺CD4⁺ T helper cells, CD8⁺ T cells, and TFH cells in healthy subjects and CLL patients.

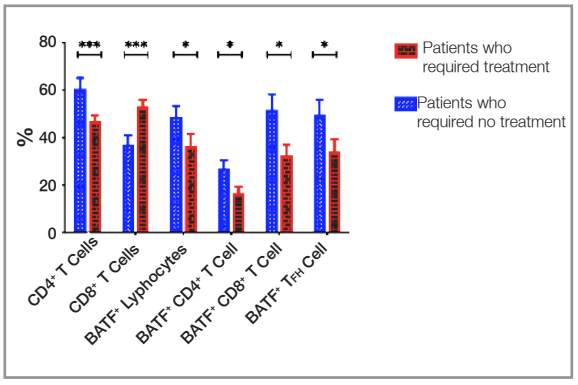

Figure 4. The comparison of CD4⁺ T cells in CD3⁺ T cells, CD8⁺ T cells in CD3⁺ T cells, BATF levels of lymphocytes, CD3⁺CD4⁺ T helper cells, CD8⁺ T cells, and TFH cells between patients who required treatment or those who did not.

Correlation Between BATF Levels and CLL Cell Populations

There was a negative correlation between BATF levels in CD4⁺ T cells and the count of CD5⁺CD19⁺ B-CLL cells (p< 0.0001, R: -0.823), however a positive correlation was found between BATF level in CD19⁺ cells and the level of TFH cells (p= 0.007, R: 0.453). Additionally, BATF levels in CD19⁺ cells were positively correlated with the count CD5⁺CD19⁺ B-CLL cells (p= 0.001, R: 0.53). No statistically significant difference was observed in BATF levels in CD19⁺B, CD3⁺ T, CD3⁺CD4⁺ helper T, CD3⁺CD4⁻ cytotoxic T and TFH cells between patient groups. Similarly, no significant differences in BATF levels were detected among patient groups according to two staging systems.

Long-Term Follow-Up and Treatment Status

Patients were followed for a long-term period (from 2016 to 2024) to evaluate their treatment status. While 15 patients did not receive any treatment, while 19 patients underwent treatment with cyclophosphamide, ibrutinib, endoxan, rituximab, R-benda, R-CHOP, FCR or venotoclax at different time points after blood sample collection (Table 2). To evaluate the potential role of BATF levels as a biomarker for determining the initiation of treatment in the long term, patients were divided into two groups based on whether they received treatment.

Relationship Between T Cell Subsets and Treatment Requirement

In this study, CD4⁺ T helper, CD8⁺ cytotoxic T and TFH cells were reanalyzed according to treatment status. CLL patients who required treatment had reduced CD4⁺ T helper and elevated CD8⁺ cytotoxic T cells in T cells compared with the patients who required no treatment (p= 0.002 and p= 0.002, respectively) (Figure 4). No statistically significant difference was found in TFH and CD5⁺CD19⁺ B cells in patient groups in accordance with the treatment status. However, TFH cells was positively correlated with CD5⁺CD19⁺ B cells in patients who required treatment (p= 0.001, R: 0.701). Lower BATF levels were found in lymphocytes, CD4⁺ T helper, CD8⁺ cytotoxic T and TFH, cells in patients who required treatment than the levels in patients who required no treatment (p= 0.03, p= 0.01, p= 0.03, and p= 0.04, respectively) (Figure 4).

DISCUSSION

BATF is a transcription factor which is predominantly expressed in T and B lymphocytes, and has a role in differentiation of CD4⁺ T cells, TFH cells, effector CD8⁺ T cells, adipose resident regulatory T cells, and also B cell for class switching by directly inducing the expression of AID, IL-21, IL-17 and miR-155.[14,28-32] Some cells and molecules affected by BATF are known to play a role in the pathogenesis of CLL. Recent studies have demonstrated

that CLL patients exhibit increased expression of IL-17, AID, and miR-155, as well as higher proportions of Th17 and TFH cells.[7,33,34] However, the studies on *BATF* in CLL patients are limited. Mittal et al. analyzed the gene expression profiling of purified CLL cells and showed the increased *BATF* mRNA expression in CLL patients using microarray methods.[35] *BATF* mRNA expression was also shown to have elevated in CLL cell line.[36] Similarly, higher *BATF* mRNA expression in whole blood of CLL patients were also found compared to the levels in healthy subjects in this study. Additionally, higher BATF levels in B, T, and TFH cells of CLL patients was observed in flow cytometry in this present study. Given that BATF regulates the expression of numerous genes of malignant B-CLL cells associated with the pathogenesis of CLL cells, a positive correlation between BATF levels and malignant B cells was detected in line with this data. These findings might suggest that BATF may be a notable molecule in malignant B-CLL cells.

Chronic lymphocytic leukemia is generally an indolent disease with a longer survival time, leading to the monitoring of the majority of patients without treatment.[1] However, in a subset of patients, treatment indications may develop over time. Predicting the patients that will require treatment and identifying the biomarkers that may be useful are crucial. Based on this information, the clinical follow up of the patients were pursued from 2016 to 2024 after the study. The BATF levels were found lower in patients who required treatment. The role of BATF in $CD8^+$ cytotoxic T lymphocytes has not yet been fully understood. Some studies suggest that BATF induces an exhausted phenotype in $CD8^+$ T lymphocytes, while others suggest that it promotes an effector memory phenotype.[37-40] $CD8^+$ T lymphocytes are known to play a primary role in the response against malignant cells. In our study, $CD3^+CD4^-$ cells were determined as $CD8^+$ T cells, we found that BATF levels were lower in the cells of patients who required treatment. Despite the increased presence of $CD8^+$ T cells capable of lysing malignant B cells in patients requiring treatment, considering of the studies which suggest BATF as a possible effector phenotype in $CD8^+$ T lymphocytes, the lower expression of BATF in these cells suggests that $CD8^+$ T cells may not have differentiated into an effector phenotype and may remain rather in an exhausted phenotype. This might have suggested that $CD8^+$ T cells may be insufficient in lysing malignant B cells, potentially contributing to the need for initiating treatment in these patients.

Recent studies have shown that increased IL-17 and Th17 levels are significantly correlated with lower Rai stages and indolent disease phases, and serum IL-17 levels have been reported to affect the time of the first treatment.[7] IL-17 is primarily secreted by $CD4^+$ helper T cells. We found the BATF levels in $CD4^+$ helper T cells negatively correlated with $CD5^+CD19^+$ malignant B cells in our study. Additionally, higher BATF levels were observed in $CD4^+$ T cells of patients who did not require treatment. Our findings suggest that BATF may promote the differentiation of $CD4^+$ T cells towards the Th17 lineage, and in line with the literature, may contribute to delayed treatment initiation by increasing IL-17 levels.

Our study also has some limitations. Firstly, this study was conducted with a small patient cohort. Further studies with larger number of patients with CLL may allow for identification of the role of BATF in CLL pathogenesis. Additionally, BATF mRNA expression was analyzed in whole blood. In order to better demonstrate the role of BATF in CLL, BATF mRNA expression may be analyzed in B or T sorting cells. Recent studies suggest that the deletion of the Regnase-1 gene, leading to increased levels of BATF, enhances anti-tumor activity. In addition, it has been reported that BATF, in collaboration with IRF4, might possess the capacity to steer T cells away from exhaustion-like programming.[38] Other molecules such as IRF4 which cooperate with BATF were not analyzed in this study. Investigation of the molecules that interact with BATF could provide a deeper understanding of the role of BATF in CLL.

In conclusion, BATF expression was found to be elevated in $CD19^+$ B, $CD4^+$ T, $CD8^+$ T and TFH cells of CLL patients. Additionally, BATF levels in $CD19^+$ B cells were positively correlated with $CD5^+CD19^+$ B-CLL cells, suggesting a potential link between BATF and malignant B cell populations. The decreased levels of BATF in $CD8^+$ T cells in patients who received treatment might have been associated with T cell exhaustion, leading to

a diminished cytotoxic effect of $CD8^+$ T cells on malignant cells. Additionally, the presence of increased $CD8^+$ T cell with lower BATF levels in CLL patients could provide insights into which patients under long-term follow-up might require treatment at a later stage. These findings suggest that BATF could serve as a potential biomarker for predicting treatment necessity in CLL. Given the current role of BATF with some molecules associated with the pathogenesis of CLL, our findings provide the impression that BATF might play a role in CLL biology and could be further investigated as a therapeutic target.

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