Can Apela be a Novel Target in the Treatment of Chronic Lymphocytic Leukaemia?

Didar Yanardag Acik  didaryanardag@gmail.com  
Corresponding Author  
ORCiD: 0000-0001-7282-0188

Mehmet Bankir  
Adana Numune Egitim ve Arastirma Hastanesi

Filiz Alkan Baylan  
Kahramanmaras Sutcu Imam Universitesi Tip Fakultesi

Bilal Aygün  
Adana Numune Egitim ve Arastirma Hastanesi

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Abstract

Background: It has been shown that bcl2, bcl-XL and mcl-1 protein levels are high in chronic lymphocytic leukemia cells, and resultantly, apoptosis does not occur chronic lymphocytic leukemia cells. Apelin and apela are two peptide ligands for a class A G-protein coupled receptor called apelin receptor. Studies have shown that apella inhibits apoptosis by inhibiting apoptotic proteins and activating anti-apoptotic proteins. Proteins and genes involved in apoptosis are valuable for targeted cancer therapy. We hypothesized that serum levels may be increased in patients with chronic lymphocytic leukemia based on the antiapoptotic effect of apelin. We compared serum apelin levels of healthy volunteers and patients with chronic lymphocytic leukemia. We aimed to draw attention to a new molecule worthy of research in targeted cancer treatment.

Methods: 42 untreated CLL patients and 41 healthy volunteers were included in the study. Serum Apela levels were measured by using enzyme-linked immunosorbent assay (ELISA) kits (Dhanghai Sunred Biological Technology co. Ltd), automated ELISE reader (Thermo Scientific, FINLAND) and computer program (ScanIt for Multiscan F.C.2.5.1) in accordance with the manufacturer’s instructions. Statistical analysis was made by Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL) ve MedCalc programs. Apela and variables related to CLL were correlated with Spearman correlation anlysis test. ROC analysis and Youden index method were used to determine a cut off point for apela. All p-values were 2-sided with statistical significance at 0.05 alpha levels.

Results: In our study, we found that serum apela levels were significantly higher in patients with CLL. Conclusions: This study highlights that apela targeting may be a potential therapeutic option for
Background

Chronic lymphocytic leukaemia (CLL) is the most frequent type of leukaemia in adults worldwide (1). It is a malignancy characterised by accumulation of small, neoplastic CD5+ B cells with a mature appearance in blood, bone marrow and secondary lymphoid tissues, lymphadenopathy and splenomegaly (2). In contrast to malignant cells of other B lymphocytes, the majority of CLL cells are arrested in the G0/G1 cell transformation phase because they do not possess proliferative capacity. Therefore, CLL does not occur as a result of excessive B cell proliferation but because of defective apoptosis (3). The mechanism of apoptosis is complex and involves two separate regulatory pathways: the intrinsic and extrinsic pathways. The intrinsic pathway is regulated by the bcl-2 family. Bcl-2 itself is an anti-apoptotic protein and is part of a complex including MCL-1, BCL-XL, BCL-W and BFL-1, all of which support cell survival. The bcl-2 family members, including BAX and BAK, which are homo-oligomerized when activated and regulate outer mitochondrial membrane permeability, cause irreversible caspase activation and subsequently apoptotic cell death (4).

Studies have suggested that bcl 2, bcl-XL and mcl-1 protein levels are high in CLL cells, and therefore, apoptosis does not occur in CLL cells (3,4).

The clinical course of CLL considerably varies. This variability has been linked to mutations in TP53. TP53 is the most important predictor of response to therapy and prognosis. It has been found that TP53 undergoes mutation in half of all human cancer cases and that loss of regulatory function of TP53 leads to oncogenesis. Loss
of function of TP53 is considered to be an important event in tumour formation and is also associated with chemotherapy resistance and poor prognosis in many cancers (5). Therefore, mechanisms that activate or inhibit TP53 have been the focus of research in targeted cancer therapy.

Apelin and apela (ELABELA/ELA/Toddler) are two peptide ligands for a class A G-protein coupled receptor called apelin receptor (AR/APJ/APLNR). These ligands function by binding to this receptor; this is known as the apelinergic system (Apelin/APJ system). The binding of both endogenous peptides to AR results in similar physiological effects (6). It is well known that the Apelin/APJ system can regulate apoptosis in various cell types and subsequently mediate the formation and development of related diseases. Recent evidence suggests that the Apelin/APJ system affects apoptosis in various diseases through different signalling pathways. Pre-treatment of cardiomyocytes with apelin-13 effectively inhibits apoptosis caused by glucose withdrawal and can significantly increase Akt and mTOR phosphorylation by upregulating Bcl-2 and downregulating Bax and cleaved caspase-3 expression.

The Apelin/APJ system also upregulates the expression of Bcl-2 and downregulates the expression of Bax protein (7-11).

Apela (also known as Ende, Elabela and Toddler) was first identified in a gene expression panel for new mouse endoderm-specific genes and is evolutionally conserved among vertebrates. In zebrafish, loss of apela disrupts mesendodermal cell movement during gastrulation, resulting in defects in endoderm differentiation and heart development and in posterior malformations. Apela acts as an endogenous ligand for APLNR, its G-protein-linked receptor, and apela and APLNR have been shown to direct angioblast migration to control the vascular pattern in
zebrafish embryos (12-14). Apela is highly expressed in human blastocysts prior to implantation and contributes to the pluripotency of human embryonic stem cells (hESCs) via an alternative receptor (15).

The non-coding region of apela has been shown to play a role in the regulation of apoptosis induced by p53-mediated DNA damage in mouse embryonic stem cells. Apela downregulates the interaction between heterogeneous nuclear ribonucleoprotein L (hnRNPL) and p53 (16).

In this study, we aimed to investigate the relationship between apela and CLL because the apelinergic system blocks the caspase system that induces apoptosis and validate the anti-apoptotic effects of apela that have been demonstrated in previous studies.

Methods

This prospective study was approved by the ethics committee, and 42 patients diagnosed between 2012 and 2019 at Adana Numune Training and Research Hospital and followed up without treatment and 41 healthy controls were evaluated. Written informed consent was obtained from patients and healthy volunteers. The diagnosis of CLL was made according to iw CLL (17) and the patients were staged according to Rai staging system (18). The data included gender; age; white blood cell count (WBC); lymphocyte count; hemoglobin (Hb) level; platelet count; presence of Del13q14, p53. Blood samples were drawn from the subjects and centrifuged at 4000 rpm for 10 minutes and stored at -80 °C as serum until use. Serum APELA levels were measured by by using enzyme-linked immunosorbent assay (ELISA) kits (Dhanghai Sunred Biological Technology co. Ltd), automated ELISE reader (Thermo Scientific, FINLAND) and computer program (ScanIt for Multiscan F.C.2.5.1) in
accordance with the manufacturer’s instructions. Sensitivity was 0.118 ng/ml and assay range was 0.15 ng/ml – 40 ng/ml. Intra-Assay \%CV was <\%10 and inter-assay \%CV was <\%12. The results were expressed as ng/ml.

**Statistical analysis**

Statistical analysis was made by Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL) ve MedCalc programs. The normality of the data was evaluated by Kolmogorov-Smirnov test. Data were described as numbers and percentage or median and range or mean ± standart deviation, when appropriate. T test (for normally distribubted data) and Mann Whitney U test for continuous values to compare the numeric values between the patient and control groups. \( \chi^2 \) Fisher’s exact test was used for evaluating categorical values. Apela and variables related to CLL were correlated with Spearman correlation analysis test. ROC analysis and Youden index method were used to determine a cut off point for apela. All p-values were 2-sided with statistical significance at 0.05 alpha levels.

**Results**

The study population comprised 83 subjects: 41 in the control group and 42 with CLL. There was no significant difference between the CLL and control group in mean age (63.9 ± 9.8 vs. 61.7 ± 10.2, \( P = 0.332 \)). The ratio of male patients was higher in the CLL group than in the control group (66.7% vs. 39%, \( P = 0.016 \)) (Table 1). There was no significant difference between the CLL and control group in mean haemoglobin levels (12.5 ± 2.2 g/dL vs. 12.7 ± 2 g/dL, \( P = 0.707 \)) and median neutrophil levels (5.5 \( \times \) 10\(^3\)/µL vs. 4.6 \( \times \) 10\(^3\)/µL, \( P = 0.078 \)). However, median white
blood cell (WBC) count \((27.1 \times 10^3 \text{ cells/µL vs. } 7.7 \times 10^3 \text{ cells/µL, } P < 0.001)\),
median lymphocyte count \((21.3 \times 10^3 \text{ cells/µL vs. } 2.1 \times 10^3 \text{ cells/µL, } P < 0.001)\) and
median apela levels \((6.7 \text{ ng/ml vs. } 2 \text{ ng/ml, } P < 0.001)\) were found to be higher in
the CLL group than in the control group (Figure 1), whereas the median platelet
level was lower in the CLL group than in the control group \((200 \times 10^3/\mu\text{L vs. } 253 \times 10^3/\mu\text{L, } P = 0.008)\) (Table 1).
In the control and CLL groups, the apela level did not exhibit a significant
correlation with gender and age (Table 2).
The disease duration was 2–84 months in the CLL group, and the median disease
duration was 24 months. Further, 23.8% of the patients \((n = 10)\) had stage 2, 14.3%
\((n = 6)\) had stage 3 and 7.1% \((n = 3)\) had stage 4 disease. The direct coombs (DC)
test was performed in all patients with CLL, and 11.9% \((n = 5)\) were positive. The
p53 test was performed in 21 patients, and 28.6% \((n = 6)\) were positive. The del13q
test was performed in 14 patients, and 64.3% \((n = 9)\) were positive.
Among patients with CLL, apela levels did not significantly differ according to the
disease stage and between patients with positive and negative DC test results,
patients with positive and negative p53 test results and between patients with
positive and negative delq13 test results (Table 3).
There was a positive correlation between apela levels and WBC count \((r = 0.357, P
= 0.001)\) and lymphocyte count \((r = 0.362, P = 0.001)\) in the study population
(Figure 2). No correlation was found between apela levels and other laboratory
findings. In patients with CLL, there was no significant relationship between apela
levels and disease duration, stage and laboratory findings (Table 4).
In the multivariate logistic regression model, gender, WBC count, platelet levels and
apela levels were found to be associated with CLL. Furthermore, WBC count and apela levels were identified as independent risk factors for predicting CLL (WBC: OR = 1.58, P < 0.001; apela: OR = 1.38, P < 0.001) (Table 5).

The cut-off value for WBC in predicting CLL was found to be >13.9, with 92.9% sensitivity and 97.6% specificity (+PV: 97.5%, -PV: 93%, AUC ± SE = 0.965 ± 0.023, P < 0.001). The cut-off value for apela level in predicting CLL was found to be >5.34, with 66.7% sensitivity and 75.6% specificity (+PV: 73.7%, -PV: 68.9%, AUC ± SE = 0.738 ± 0.054, P < 0.001) (Figure 3).

In patients with CLL, the ratio of DC-negative patients was found to be higher in patients with an apela level >5.34 (ng/ml) compared with those with an apela level of ≤5.34 (92.9% vs. 57.1%, P = 0.011). In patients with CLL, there was no significant relationship between patients with an apela level >5.34 (ng/ml) and patients with an apela level of ≤5.34 (ng/ml) in demographic parameters and other clinical findings (Table 6).

Discussion

Previous studies have shown that apela possesses anti-apoptototic activity (15,19). Although the role of apela in cancer has been investigated in a limited number of studies (20, 21), several studies have shown that apelin, which is the other endogenous ligand of APRLN, is overexpressed in many tumour tissues and cell lines, and the apelin/APLNR system plays a role in the regulation of cancer cell growth and migration (22-24).

In the present study, Apela levels were significantly higher in patients with CLL than in control group patients. This finding supports the anti-apoptotic effects of apela and the apelinergic system reported in the literature.
Seo et al. showed that DNA damage-induced hnRNP L upregulates *p53* expression (25).

Li et al. showed that Apela downregulates the interaction between hnRNPL and *p53* (26), resulting in an anti-apoptotic effect. Additionally, Ganguly et al. reported increased apela gene expression levels in glioblastoma cells and that an association exists between upregulated expression of Apela and poor prognosis (21). Yi et al. reported increased apela expression levels in ovarian cancer cells. Disruption of apela expression in these cell lines suppressed cell growth, cell migration and cell cycle progression. They showed that apela exerted this effect independently of APLNR, affecting cell growth and cell cycle progression in a *p53*-dependent manner. Loss of apela in cells expressing high levels of *p53* caused a decrease in cell number due to cell death, and this resulted from *p53*-induced cell apoptosis (20). Mouse double minute 2 (MDM2) is a critical negative regulator of tumour suppressor *p53* and plays a key role in controlling its transcriptional activity, protein stability and nuclear localisation. MDM2 expression is upregulated in many cancers, resulting in a loss of *p53*-dependent activities, such as apoptosis and cell cycle arrest (27). The PI3K/Akt signalling pathway has been shown to play a critical role in the tumourigenesis of haematopoietic cells. Activation of the PI3K/Akt pathway occurs even in the early stages of tumour development, and it correlates with poor prognosis and therapeutic resistance in various human cancers (15, 28). Apela activates the PI3K/AKT/mTORC1 signal to promote the progression of hESC cell cycle and protein translation and blocks stress-induced apoptosis. These pathways are the main signals reported to be correlated with apoptosis. MDM2 also inhibits *p53* through this pathway. It has been suggested that the apelinergic system may inhibit apoptosis through these common pathways (7-11, 28).
hnRNPC is a negative regulator of p53. A previous study showed that the 1-41 p53 region, which is the region where p53 binds to Mdm2, also interacts with hnRNPC. These results show that hnRNPC may be synergistic with Mdm2 in regulating p53 stability. Doxorubicin competes with p53 for binding to the RNA recognition motif of hnRNPC, thereby enhancing p53 stability and triggering p53-dependent apoptosis (29). Apela, which has been shown to possess anti-apoptotic activity, has been shown to interact with the CXCR4a signalling pathway, one of the chemokines (15, 19). Chemokines are produced by cancer-associated fibroblasts, a component of stromal cells, and affect metastatic potential and site-specific spread of cancer cells. The stromal cell-derived factor-1 (SDF-1/CXCL12) belongs to the family of CXC chemokines. The effects of CXCL12 in many cancer types, including its role in promoting local invasion and distant metastasis from lung cancer metastasis, have been described (30-32). Wang et al. showed that CXCL12 blocks apoptosis in human adenocarcinoma cell line via CXCR4. They observed that the expression levels of Bcl-2 and bcl-xl in the adenocarcinoma cell line increased with CXCL12 therapy and decreased with CXCR4 antagonist and JAK2 inhibitor therapy (33). In summary, apela and the apelinergic system have been shown to inhibit apoptosis in several steps (via bcl-2, bcl-xl, mdm2, hnRPLN, p53, and PI3K/Akt/mTORC1). Based on these results, it can be suggested that apela and the apelinergic system play a central role in the pathogenesis of CLL.

In the present study, we showed that serum apela levels were significantly high in patients with CLL. This finding indicates that apela contributes to the development of CLL, which is consistent with the findings of other studies in the literature.

Venetoclax is a bcl-2 inhibitor and idasanutlin is a MDM2 inhibitor, and both are indicated for use in CLL. Venetoclax + idasanutlin have been suggested to be an
effective treatment for relapsed/refractory acute myeloid leukaemia (AML) (34).

However, inhibition of apela or the apelinergic system will exert the effect of both venetoclax and idasanutlin. In other words, inhibition of the apelinergic system alone can provide a treatment as effective as venetoclax and idasanutlin or even a combination of the two. Yi et al. showed that human apela can downregulate p53 protein levels and activity in cancer cells instead of working as a p53 activator. Although ovarian cancer cells are typically normal type p53, no studies have assessed whether there is a correlation between p53 mutation status and apela expression levels in ovarian cancer (20).

Because the number of patients with TP53 mutation was insufficient in the present study, we could not perform a statistically significant evaluation. However, future studies evaluating a sufficient number of patients will be valuable for CLL, in which TP53 mutations occur frequent. The results of our study provide evidence that apela and the apelinergic system can be valuable in targeted therapy and may also be useful in predicting patient prognosis, response to treatment and follow-up. More comprehensive studies are needed to address these issues.

Conclusions

This study highlights the effects of apela on CLL and emphasizes that apela targeting may be a potential therapeutic option for treating CLL.

Abbreviations

CLL: chronic lymphocytic leukemia; WBC: white blood cell count; Hb: hemoglobin;
PLT: platelet; ELISA: enzyme-linked immunosorbent assay; OR: Odds ratio; CI:
Confidence intervals
Declarations

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Not applicable.

Data availability
The authors declare that all other data supporting the findings of this study are available within the article and its Supplementary Information Files. Additional files

Authors’ contributions
The author(s) have made the following declarations regarding their contributions:

Didar Yanardag Acik: Designed the study, collected data and approved the final manuscript. Mehmet Bankir: Informing patients and volunteers and obtaining their consent. Prepared the samples.

Filiz Alkan Baylan Performed the experiments.

Bilal Aygun: Analyzed the data.

All authors read and approved the final manuscript.

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Availability of data and materials
The datasets generated for this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
Ethics committee approval was received. The non-invasive clinical research ethics committee of T. C. Çukurova University Faculty of Medicine convened on 5 October 2019 and approved the study. Written informed consent was obtained from patients and healthy volunteers. The ethics committee decision is attached.
Consent for publication

Not applicable.

Competing interests

All authors are aware of the consent and agree with the submission. The authors declare no conflict of interest or competing interests. No changes will be made to the authors.

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Figure 2. Relationship between apela levels and neutrophil levels

Figure 3. Evaluation of the diagnostic performance of apela level in predicting CLL

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Figure 1

Mean apela level in the control and CLL groups
Figure 2

Relationship between apela levels and neutrophil levels
Figure 3

Evaluation of the diagnostic performance of apela level in predicting CLL

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