RESEARCH ARTICLE

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A New Scoring System for the Evaluation of Ibrutinib-Associated Arrhythmias in Chronic Lymphocytic Leukemia: The ACEF Score

Kronik Lenfositik Lösemide İbrutinib ile İlişkili Aritmilerin Değerlendirilmesinde Yeni Bir Skorlama Sistemi: ACEF Skoru

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Abstract

Objective: Bruton tyrosine kinase inhibition in cardiac tissue causes inhibition of the PI3K-AKT signaling pathway, which is responsible for protecting cardiac tissue during stress. Therefore, there is an increase in the risk of arrhythmia. This study explores the prediction of that risk with the Age-Creatinine-Ejection Fraction (ACEF) score as a simple scoring system based on the components of age, creatinine, and ejection fraction.

Materials and Methods: Patients diagnosed with chronic lymphocytic leukemia (CLL) and receiving ibrutinib treatment for at least 1 year were evaluated with echocardiography and Holter electrocardiography and the results were compared with a control group of CLL patients who had not received treatment. ACEF score was calculated with the formula age/left ventricular ejection fraction+1 (if creatinine >2.0 mg/dL).

Results: When the arrhythmia development of the patients was evaluated, no statistically significant difference was found between the control and ibrutinib groups in terms of types of arrhythmias other than paroxysmal atrial fibrillation (PAF). PAF was found to occur at rates of 8% versus 22% (p=0.042) among ibrutinib non-users versus users. For patients using ibrutinib, an ACEF score of >1.21 predicted the development of PAF with 77% sensitivity and 75% specificity (area under the curve: 0.830, 95% confidence interval: 0.698-0.962, p<0.001).

Conclusion: The ACEF score can be used as a risk score that predicts the development of PAF in patients diagnosed with CLL who are scheduled to start ibrutinib.

Keywords: Ibrutinib, ACEF score, Chronic lymphocytic leukemia, Arrhythmia

Öz

Amaç: Kardiyak dokuda Bruton tirozin kinaz inhibisyonu, stres sırasında dokunun korunmasından sorumlu olan PI3K-AKT sinyal yolunun inhibisyonuna neden olur. Bu nedenle aritmi riskinde bir artış vardır. Bu çalışma, yaş, kreatinin ve ejeksiyon fraksiyonu komponentlerini temel alan ve basit bir puanlama sistemi olan Yaş-Kreatinin-Ejeksiyon Fraksiyonu (ACEF) skoru ile bu riskin tahmin edilebilmesini araştırmaktadır.

Gereç ve Yöntemler: Kronik lenfositik lösemi (KLL) tanısı alan ve en az 1 yıldır ibrutinib tedavisi alan hastalar ekokardiyografi ve Holter elektrokardiyografi ile değerlendirildi ve sonuçlar tedavi almayan KLL hastalarından oluşan kontrol grubuyla karşılaştırıldı. ACEF skoru, yaş/sol ventriküler ejeksiyon fraksiyonu+1 (kreatinin >2,0 mg/dL ise) formülüyle hesaplandı.

Bulgular: Hastaların aritmi gelişimi değerlendirildiğinde paroksismal atriyal fibrilasyon (PAF) dışındaki aritmi türleri açısından kontrol ve ibrutinib grupları arasında istatistiksel olarak anlamlı bir fark bulunmadı. PAF, ibrutinib kullanmayanlar ile kullananlar arasında %8'e karşı %22 (p=0,042) oranında meydana gelmekteydi. İbrutinib kullanan hastalarda ACEF skorunun >1,21 olması, PAF gelişimini %77 duyarlılık ve %75 özgüllükle öngörmekteydi (eğri altındaki alan: 0,830, %95 güven aralığı: 0,698-0,962, p<0,001).

Sonuç: ACEF skoru, KLL tanısı alan ve ibrutinib başlanması planlanan hastalarda PAF gelişimini öngören bir risk skoru olarak kullanılabilir.

Anahtar Sözcükler: İbrutinib, ACEF skoru, Kronik lenfositik lösemi, Aritmi

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Introduction

Ibrutinib is an agent that irreversibly blocks the Bruton tyrosine kinase (BTK) pathway, which plays an important role in B-cell malignancies [1]. It prolongs disease-free survival and prevents relapses in cases of B-cell malignancies such as chronic lymphocytic leukemia (CLL), mantle cell lymphoma, and Waldenström macroglobulinemia [2,3,4]. Although the primary target of ibrutinib is BTK, its effect are non-specific. It has been shown to impact many BTK-like pathways in different tissues and organs [3]. Therefore, alongside its clinical benefits, many side effects and toxicities have been observed [4,5,6].

BTK inhibition in cardiac tissue causes inhibition of the PI3K-AKT signaling pathway, which is responsible for protecting cardiac tissue during stress. Despite initially successful clinical data, subsequent studies demonstrated an association between ibrutinib and atrial fibrillation (AF). The risk of AF increases with ibrutinib treatment from the first months [7]. The pathogenesis of ibrutinib-associated AF (IAAF) is unclear, although inhibition of the PI3K-AKT signaling pathway with factors such as transient erythroblastopenia of childhood tyrosine kinase, which is especially highly produced in atrial tissues, is suspected by direct drug action. Furthermore, increases in atrial structural disorders and calcium metabolism disorders with ibrutinib in mouse model studies support the hypothesis that the PI3K-AKT signaling pathway is suppressed in patients with structural disorders [8,9,10,11].

The Age-Creatinine-Ejection Fraction (ACEF) score is a simple scoring system that can be calculated using the components of age, creatinine, and ejection fraction. It has been associated with satisfactory predictive value not only for short- and long-term mortality but also for major adverse cardiovascular events [12]. It was originally developed for the risk stratification of patients undergoing elective cardiac surgery. In later studies, it was also used to predict adverse cardiac events and the development of contrast-associated nephropathy in patients undergoing percutaneous coronary angioplasty. The relationship between ACEF risk scores and atrial and ventricular arrhythmia has also been shown [13].

The aims of this study were to investigate the relationship between the ACEF risk score and IAAF, to identify CLL patients with a high likelihood of IAAF prior to the initiation of ibrutinib treatment, and to determine whether the ACEF score can be used as a risk score to guide the treatment planning and follow-up of CLL patients.

Materials and Methods

Ethics Committee Approval

The research was begun after receiving approval from the Bakırçay University Non-Interventional Clinical Research Ethics Committee (approval number: 837, date: 18.01.2023).

Patient Population and Data Acquisition

The research was designed as a retrospective and cross-sectional study. The cases of patients diagnosed with CLL and followed in the hematology clinic between November 2018 and August 2021 were reviewed. Patients younger than 18 years of age, those using antiarrhythmic drugs for any reason, and those with severe renal insufficiency, severe hepatic insufficiency, active solid organ malignancy, history of previous stroke, AF on electrocardiography before treatment, or severe mitral stenosis, severe mitral regurgitation, or hypertrophic cardiomyopathy on echocardiography predisposing to AF were excluded. The included patients were divided into two groups: those who received ibrutinib treatment and those who did not. Patients receiving first- or second-line therapy were included in the ibrutinib arm of the study while the control group comprised patients who were followed without treatment. In addition to not receiving ibrutinib, they did not receive non-BTK treatment.

Demographic data and biochemical parameters at diagnosis were recorded for both groups. ACEF scores at the time of diagnosis were calculated using the following formula: ACEF: age/left ventricular ejection fraction + 1 (if creatinine >2.0 mg/dL) [14]. A 24-h Holter electrocardiography examination was performed for patients in both groups. The Holter electrocardiography data of the patients and all detected arrhythmia types were recorded.

Statistical Analysis

IBM SPSS Statistics 25.0 was used for all statistical analyses. The compliance of numerical variables to normal distribution was examined using the Kolmogorov-Smirnov test. Numerical variables were presented as means and standard deviations. To make comparisons between two groups of numerical variables, the independent-samples t-test was used in the event of normal distribution and the Mann-Whitney U test was used for variables that did not demonstrate normal distribution. Categorical variables were reported as numbers (n) and percentages (%). Relationships between categorical variables were examined with the Pearson chi-square or Fisher exact test. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off value of the ACEF risk score. In all analyses, values of $p<0.05$ were accepted as significant.

Results

Data reflecting the patients' demographic and clinical information and components of the ACEF score are shown in Table 1. There were no statistically significant differences between the groups except for alcohol use and systolic blood pressure values among the parameters that may cause AF based on the data obtained.

When the arrhythmia development of the patients was evaluated (Table 2), no statistically significant difference was

Table 1. Baseline clinical characteristics.

	Control group (n=60)	Ibrutinib group (n=58)	p
Female, n (%)	23 (38.3)	24 (41.3)	0.851
BMI, kg/m^2	26.88±3.37	27.41±3.67	0.151
Hypertension, n (%)	40 (66.6)	37 (63.7)	0.847
Diabetes mellitus, n (%)	21 (35)	19 (32.7)	0.847
Hyperlipidemia, n (%)	19 (31.6)	22 (37.9)	0.563
Heart failure, n (%)	3 (5)	6 (10.3)	0.318
CHD, n (%)	19 (31.6)	12 (20.6)	0.212
Thyroid disease, n (%)	9 (15)	14 (24.1)	0.250
COPD, n (%)	10 (16.6)	9 (15.5)	1.000
CKD, n (%)	8 (13.3)	7 (12.1)	1.000
PAD, n (%)	1 (1.6)	3 (5.2)	0.360
Smoking, n (%)	29 (48.3)	23 (39.6)	0.360
Alcohol use, n (%)	17 (28.3)	7 (12.1)	**0.039**
Systolic BP, mmHg	130.66±24.29	141.32±17.79	**0.007**
Diastolic BP, mmHg	73.91±16.66	78.10±9.15	0.093
ACEF score components			
Age, years	66.60±13.23	67.08±11.39	0.831
LVEF, %	59.21±7.01	59.62±6.17	0.740
Creatinine, mg/dL	1.13±0.60	1.08±0.34	0.726
ACEF score	1.18±0.28	1.19±0.44	0.837

BMI: Body mass index; CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; PAD: peripheral artery disease; BP: blood pressure; ACEF score: Age-Creatinine-Ejection Fraction score; LVEF: left ventricular ejection fraction.

Table 2. Arrhythmia development by groups.

	Control group	Ibrutinib group	p
Arrhythmia, n (%)	42 (70)	40 (69)	1.0
Ventricular extrasystole, n (%)	17 (28)	21 (36)	0.432
PAF, n (%)	5 (8)	13 (22)	**0.042**
Atrial premature beats, n (%)	26 (43)	33 (56)	0.197
Non-sustained VT, n (%)	4 (6)	3 (5)	1.0
Atrioventricular extrasystole, n (%)	27 (45)	24 (41)	0.714
Supraventricular tachycardia, n (%)	2 (3)	5 (8)	0.268
VT, n (%)	0 (0)	1 (2)	0.492

PAF: Paroxysmal atrial fibrillation; VT: ventricular tachycardia.

found between the control and ibrutinib groups in terms of arrhythmia, ventricular extrasystole, atrial premature beats, non-sustained ventricular tachycardia, atrioventricular extrasystole, and supraventricular tachycardia or ventricular tachycardia development. However, there was a statistically significant increase in PAF attacks in the group receiving ibrutinib compared to the control group (13 [22%] vs. 5 [8%], p=0.042).

Among the patients receiving ibrutinib, an ACEF score of >1.21 predicted the development of PAF with 77% sensitivity and 75% specificity (area under the curve in ROC analysis: 0.830, 95% confidence interval: 0.698-0.962, p<0.001) (Figure 1).

Discussion

When the predictors of IAAF were investigated in previous studies, it was remarkably shown that ibrutinib increased the risk of developing IAAF independently of the considered conditions, even in patients with AF predictors such as hypertension (HT), mitral valve disease, and coronary heart disease [15,16].

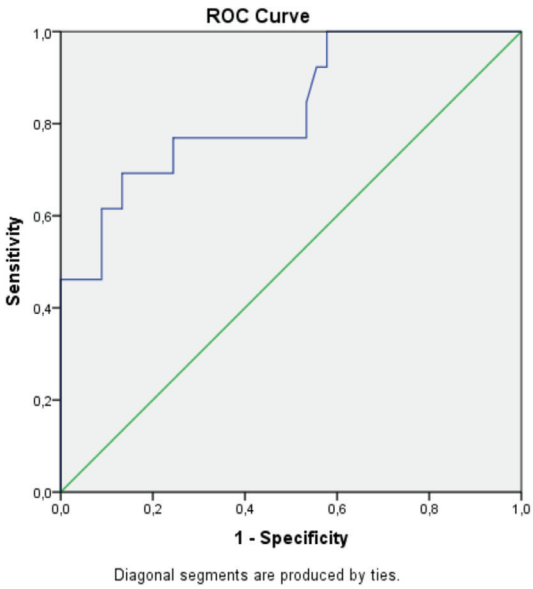

Figure 1. Receiver operating characteristic (ROC) curve analysis of the ability of the ACEF risk score to predict arrhythmia development in patients receiving ibrutinib.

The incidence of IAAF in clinical drug trials varies between 5% and 10% [17,18]. According to real-life data, the incidence of IAAF is between 16% and 38% after 2 years of follow-up [19,20]. This difference is probably due to the exclusion of patients with cardiac comorbidities in clinical studies [21]. The findings obtained in our study are consistent with real-life data in this regard.

Studies investigating risk scoring for IAAF are limited in the literature. A Mayo Clinic study of 2,292 patients investigated the association between IAAF and conventional AF risk factors such as HT, valvular heart disease, advanced age, and male sex. The incidence of IAAF development was found to be 4% in the presence of 0 or 1 risk factors, 9% in the presence of 2 or 3 risk factors, 17% in the presence of 4 risk factors, and 33% in the presence of ≥5 risk factors [22]. In another study involving 189 patients using ibrutinib for B-cell malignancies, a significant association was found between the presence of structural and functional cardiovascular diseases including HT, advanced age (>80 years), and heart failure and the development of IAAF [23].

The ACEF risk score may be an alternative tool for the prediction of IAAF in patients with CLL, as it can be easily calculated with simple parameters. Age, as the first of the ACEF risk score components, is an important risk factor for both arrhythmia development and ischemic stroke independent of arrhythmia. Structural and functional changes in the mechanical and electrical system of the heart with aging predispose to arrhythmia development [24,25]. The frequency of both atrial and ventricular arrhythmias increases with increasing age [26]. In particular, the frequency of AF increases in direct proportion to age, with its incidence being approximately 8%-10% in octogenarians [27,28].

In patients with renal failure, susceptibility to atrial and ventricular arrhythmias increases due to electrolyte imbalance, structural changes in cardiac tissue, increased myocardial fibrosis, and sympathetic reactivity [29]. In a study of patients without advanced heart failure in a chronic hemodialysis program, 86% had an arrhythmia detected by implantable cardiac monitoring.

Decreased left ventricular function is the most important predisposing factor for atrial and ventricular arrhythmias independent of coronary artery disease. A decrease in left ventricular systolic functions causes abnormal left ventricular filling and atrial remodeling, and this situation predisposes to AF. AF and heart failure with reduced ejection fraction (HFrEF) often coexist and each increases the likelihood of the other, complicating the disease course and treatment [23,30]. Patients with HFrEF and AF are generally older, have greater symptom burden and lower quality of life, and have more comorbidities than patients without AF. AF may be a marker of more advanced heart failure rather than an independent prognostic risk factor. Patients with PAF may be at higher risk than patients with permanent AF [31,32].

Study Limitations

The most important limitation of our study is that it was a retrospective and observational study. Another limitation is that only 24-h Holter electrocardiography recordings were performed for all patients. If recorders that can record for longer periods of time or implantable loop recorders are used, more AF may be detected and the specificity and sensitivity values of the ACEF score may change.

Conclusion

The ACEF score can be used as a risk score that predicts the development of PAF in patients diagnosed with CLL who are scheduled to start ibrutinib. Further large-scale studies of the predictive value of the ACEF risk score in the development of arrhythmia are needed to support our results.

Ethics

Ethics Committee Approval: The research was begun after receiving approval from the Bakırçay University Non-Interventional Clinical Research Ethics Committee (approval number: 837, date: 18.01.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: B.K., M.C.U., E.K., O.Ş.; Concept: İ.K., M.C.U., O.B.; Design: İ.K., M.C.U., O.B.; Data Collection or Processing: İ.K., B.K.; Analysis or Interpretation: B.K., E.K., O.Ş.; Literature Search: İ.K., M.C.U., M.D.; Writing: İ.K., M.C.U., M.D.

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