Visentin A. (Orcid ID: 0000-0003-0271-7200)
Autore F. (Orcid ID: 0000-0002-7868-7469)
Tedeschi A. (Orcid ID: 0000-0001-8724-2771)
Laurenti L. (Orcid ID: 0000-0002-4527-4131)

A SCORING SYSTEM TO PREDICT THE RISK OF ATRIAL FIBRILLATION IN CHRONIC LYMPHOCYTIC LEUKEMIA

A. Visentin[1,2], M. Deodato[3], F.R. Mauro[4], F. Autore[5], G. Reda[6], C. Vitale[7], S. Molica[8], G.M. Rigolin[9], F. Piazza[1,2], L. Cesini[4], A. Tedeschi[3], L. Laurenti[5], R. Cassin[6], M. Coscia[7], A. Cuneo[9], R. Foà[4], G. Semenzato[1,2], L. Trentin[1,2,*]

[1]Hematology and Clinical Immunology Unit, Department of Medicine, University of Padua, Italy. [2]Venetian Institute of Molecular Medicine, Centro di Eccellenza per la Ricerca Biomedica Avanzata, Italy. [3]Hematology Unit, Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy. [4]Hematology unit, Department of Translational and Precision Medicine, Sapienza University, Rome, Italy. [5]Hematology Institute, Fondazione Policlinico Universitario Agostino Gemelli IRCSS, Rome, Italy. [6]Hematology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore, University of Milan, Milan, Italy. [7]Division of Hematology, A.O.U. Città della Salute e della Scienza di Torino, University of Turin, Turin, Italy. [8]Department Hematology-Oncology, Azienda Ospedaliera Pugliese-Ciaccio, Catanzaro, Italy. [9]Hematology section, Department of Medical Sciences, University of Ferrara - Azienda Ospedaliera-Universitaria di Ferrara, Ferrara, Italy.

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*** Corresponding author:**
Livio Trentin, M.D.
Hematology and Clinical Immunology unit
Department of Medicine
University of Padua
Via Giustiniani 2
35128 Padova, Italy
e-mail: livio.trentin@unipd.it
phone: ++39 049-821 2298
Fax: ++39 049 8211970

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SUMMARY
Ibrutinib, the first in class of BTK inhibitor, has improved the management of patients with chronic lymphocytic leukemia. Since ibrutinib can cause atrial fibrillation in 6-16% of cases, it is clinically relevant to identify patients at higher risk to develop atrial fibrillation. Comorbidities associated with a higher risk to develop atrial fibrillation were recapitulated in a scoring system. This model proved to be a valid prognostic tool both in a general chronic lymphocytic leukemia population (n=860) and in an ibrutinib-treated cohort (n=354). Patients with score≥5 harbored the highest risk of atrial fibrillation and should be carefully monitored during ibrutinib therapy.

MAIN TEXT

The Bruton's tyrosine kinase (BTK) inhibitor (BTKi) ibrutinib has significantly improved the management of chronic lymphocytic leukemia (CLL). Although ibrutinib is generally well tolerated, it has been associated with atrial fibrillation (AF) in 6-16% of cases[1]. Most CLL patients are elderly and suffer of several comorbidities[2-3] that may trigger AF regardless of ibrutinib. Since a continuous treatment is required to achieve/maintain the benefit with BTKi, the identification of patients at high-risk of developing AF during ibrutinib is crucial. The purpose we investigated the prevalence and risk factors of AF in a cohort of ibrutinib-naive CLL, in order to define a predictive model for the development of AF and to validate it in a cohort of ibrutinib-treated patients.

We retrospectively analyzed data from 860 CLL patients untreated with or censured at the start ibrutinib, referred to the Padua University Hospital. Diagnosis of CLL fulfilled the iwCLL2008 criteria. Biological markers were analyzed as previously reported[4]. Comorbidities, time to AF (TTAF) and overall survival (OS) were evaluated as described in supplementary methods. Univariate and multivariate Cox models were run to identify independent factors associated with AF. Risk points were obtained based on the half value of hazard ratios (HR). The score for AF was calculated as the sum of each risk point. The model was then evaluated in a cohort of ibrutinib-treated patients.

Among the 860 patients from the Padua hospital, 60% were male, the median age at diagnosis was 66.8 years, 73% were Binet A stage at diagnosis and 41% required at least one treatment. A prior history of AF was present in only 21 patients (2.4%) at CLL diagnosis, while, among the remaining 839 patients without a previous history of AF, 47 (5.6%) developed AF after a median follow-up of 9.4 years (Figure 1A). Comparisons of clinico-biological variables between patients with and without AF are reported in Table1 and S2. The median OS for patients with AF was significantly shorter than that of patients without AF (12 vs 22 years, $p<0.0001$, Figure 1B).

Based on univariate and multivariate analysis (HRs and confidential intervals [CI] available in Table S1), variables associated with an increased risk of AF were: age>65 years (HR=2.80, 1 point), male gender (HR=3.07, 1 point), valvular heart diseases (HR=5.71, 2 points), cardiopathy (HR=6.30, 3 points), hypo/hyper-thyroidism (HR=5.61, 2 points), chronic lung diseases (HR=3.69, 1 point), type-2 diabetes mellitus (HR=2.25, 1 point), ≥G3 infections (HR=2.09, 1 point). A predictive model (AF score) based on the above-mentioned factors identified 4 risk-groups of patients. Although none of the 137 patients at score 0 developed AF, the 545 patients with score of 1-2 had a 10-year TTAF of 6%, while the risk for the 103 and 75 patients at score 3-4 and ≥5 was 12% and 29%, respectively ($p<0.001$, Figure 1C).

Subsequently, we applied our AF model to a validation cohort of 354 ibrutinib-treated patients referred from 8 Italian hematological centers: 64% were male, the median age at ibrutinib was 69.7 years, 25% were treatment-naive, 61% had an unmutated-IGHV status and 38% harbored TP53 abnormalities. Forty-two subjects (12%) developed AF after a median

observation of 25 months from the start of ibrutinib, with an estimated 2-year TTAF of 12% (Figure 1D). Median time to AF onset was 10 months. According to the CTCAE grading 38% were ≥G3. Patients who developed AF were older and more commonly affected by the comorbidities considered in our scoring system (Table 1). Sixteen patients (4%) were classified as AF score 0, 218 (62%) score 1-2, 73 (21%) score 3-4 and 46 (13%) at score ≥5. Our model was also able to identify patients at a higher risk of AF during ibrutinib; in fact, the 2-year risk of AF was 0%, 5%, 17% and 40% for patients with score 0, 1-2, 3-4, and ≥5 respectively ($p<0.001$, Figure 1F). Patients with a score ≥5 have a 20-fold higher risk of developing AF than the other subjects (HR 19.6, 95%CI 7-52, $p<0.0001$). The OS of ibrutinib-treated patients with AF was not inferior to that of patients who did not develop AF (2-year OS 89% and 82%, $p=0.1252$, Figure1E). Only 10/44 (23%) patients discontinued ibrutinib due to AF. Management of AF was described in supplementary results.

In the Mayo clinic database[5], a prior history of AF was present in 6% of cases at CLL diagnosis and other 6% developed it during a median follow-up of 7 years. Age, male gender, valvular heart disease and hypertension were associated with risk of incident AF in multivariate analysis. A predictive model for developing an incident AF that considered these risk-factors stratified patients into 4 subgroups with 10-year rates of AF ranging from 4% to 33%[5]. In line with data from the literature[6], in our Italian CLL population a prior history of AF was present in only 2.4% of patients. While we included chronic lung diseases and severe infections, the other variables were also present in the Shanafelt's scoring system[5]. Hypertension was not statistically significant in our cohort at univariate analysis, and was excluded from multivariate analysis. Comparison of our scoring system with the Shanafelt's model is described in supplementary results and Figure S1.

Although ibrutinib is one of the most commonly used drugs in CLL, the correct management of ibrutinib-induced AF is still of concern[7-10]. In a pooled analysis[1] of 4 clinical trials with ibrutinib, the cumulative incidence of AF was 10% and most patients (86%) did not discontinue ibrutinib. Ibrutinib treatment, prior history of AF and age >65 years emerged as independent risk factors for the development of AF. More than half of the patients with AF received anti-coagulant/platelet drugs, 51% and 2% reported low-grade and serious bleedings, respectively[1]. In the current work, the cumulative incidence of AF was 12%, most cases did not discontinue ibrutinib and 76% received anticoagulants without major bleedings nor ischemic events.

In this study, variables associated with an increased risk of developing AF were identified and recapitulated into a scoring system. Taking these data into account, patients with a score≥5 should be carefully monitored during ibrutinib treatment, or considered for venetoclax/second-generation BTKi.

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AUTHORSHIP CONTRIBUTIONS

AV designed the study, evaluated patients, performed statistical analysis and wrote the article; MD, FA, CV, FP, LC and RC provided intellectual inputs and evaluated the patients during the follow-up; FRM, SM, GMR, AT, LL, MC, AC, RF, GS, LT evaluated the patients, provided intellectual inputs and reviewed the article.

DISCLOSURE OF CONFLICTS OF INTEREST

AV received honoraria from Janssen and Abbvie. LT received research funding by Gilead and Janssen, advisory board for Roche, Shire and Abbvie. GMR received research funding by Gilead. FRM advisory board for Janssen, Shire and Abbvie. AC advisory board and speaker bureau for Roche, Abbvie, Gilead and Janssen. GS board member of Abbvie, Roche, Janssen and Celgene. RF advisory board or speaker bureau for Roche, Abbvie, Celgene, Incyte, Amgen, Janssen, Celtrion, Gilead and Novartis.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the local research ethics committee of Padua hospital and informed consent was obtained from all patients

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Table 1. Clinical-biological characteristics of ibrutinib-naive and ibrutinib-treated patients.

	PADUA CLL PATIENTS				IBRUTINIB-TREATED PATIENTS			
	All n=860	**AF n=68**	**No AF n=792**	**p values**	**All n=354**	**AF n=42**	**No AF n=312**	**p values**
Age (years)								
Median Sta. dev.	66.83 10.68	69.63 9.52	64.03 11.04	<0.0001	69.66 9.23	71.04 8.70	68.28 9.31	0.0309
Gender								
Male female	511 (59%) 349 (41%)	55 (81%) 13 (19%)	456 (58%) 336 (42%)	0.0002	226 (64%) 128 (36%)	30 (71%) 12 (29%)	196 (63%) 116 (37%)	0.3080
Therapy								
TN RR	511 (59%) 349 (41%)	39 (57%) 29 (43%)	472 (60%) 320 (40%)	0.7971	90 (25%) 264 (75%)	13 (31%) 29 (69%)	77 (25%) 235 (75%)	0.4499
FISH								
13q- N +12 11q- 17p-	249 (42%) 175 (30%) 64 (11%) 55 (9%) 47 (8%)	17 (40%) 7 (16%) 3 (7%) 8 (19%) 8 (19%)	232 (42%) 168 (31%) 61 (11%) 47 (9%) 39 (7%)	0.0061	62 (18%) 85 (24%) 36 (10%) 52 (15%) 101 (29%)	8 (19%) 9 (21%) 2 (5%) 5 (12%) 18 (43%)	54 (18%) 76 (25%) 34 (11%) 47 (16%) 83 (27%)	0.3050
TP53 abn								
normal abnormal	537 (91%) 56 (9%)	35 (81%) 8 (19%)	502 (91%) 48 (9%)	0.0515	213 (60%) 135 (38%)	23 (55%) 19 (45%)	190 (62%) 116 (38%)	0.4000
IGHV status								
U-IGHV M-IGHV	224 (40%) 333 (60%)	14 (30%) 32 (70%)	210 (41%) 301 (59%)	0.2087	216 (61%) 96 (27%)	25 (66%) 13 (34%)	191 (70%) 83 (30%)	0.7079
Valvular h.d.								
Yes no	16 (2%) 844 (98%)	5 (7%) 63 (93%)	11 (1%) 781 (99%)	0.0059	34 (10%) 320 (90%)	11 (26%) 31 (74%)	23 (7%) 289 (93%)	0.0007
Cardiopathy								
Yes no	93 (11%) 767 (89%)	30 (40%) 38 (60%)	63 (8%) 729 (92%)	<0.0001	36 (10%) 318 (90%)	11 (26%) 31 (74%)	25 (8%) 287 (92%)	0.0011
Dysthyroidism								
Yes No	16 (2%) 844 (98%)	7 (10%) 61 (90%)	9 (1%) 783 (99%)	<0.0001	32 (9%) 322 (81%)	10 (24%) 32 (76%)	22 (7%) 290 (93%)	0.0017
Chr. Lung d.								
Yes no	49 (6%) 811 (94%)	15 (22%) 53 (78%)	34 (4%) 758 (96%)	<0.0001	35 (10%) 309 (90%)	8 (19%) 24 (81%)	27 (9%) 285 (91%)	0.0496
DM2								
Yes no	98 (11%) 762 (89%)	17 (25%) 51 (75%)	81 (10%) 711 (90%)	0.0010	35 (10%) 319 (90%)	9 (21%) 32 (79%)	28 (9%) 284 (91%)	0.0266
Infections ≥g3								
Yes	115 (13%)	18 (26%)	97 (12%)	0.0024	65 (18%)	13 (31%)	52 (17%)	0.0331

no	745 (87%)	50 (74%)	695 (88%)		289 (72%)	29 (69%)	260 (83%)	
Hypertension								
Yes	315 (47%)	32 (47%)	283 (36%)	0.0672	-	-	-	-
No	545 (63%)	36 (53%)	509 (64%)		-	-	-	-
Cholesterol h.								
Yes	93 (11%)	12 (18%)	81 (10%)	0.0669	-	-	-	-
No	767 (89%)	56 (82%)	711 (90%)		-	-	-	-

AF = atrial fibrillation, TN = treatment naive, RR = realpsed or refractory, U-IGHV = unmutated status of IGHV gene (i.e. homology >98% from the germiline sequence), M-IGHV =mutated status of IGHV gene, valvular h.d.= moderate to severe valvular heart disease, dysthyroidism = hypo- and hyper-thyroidism, Ch. Lung. d. = chronic lung disease, infections ≥g3 = grade 3-5 infections according to CTCAE, cholesterol h. = cholesterol levels above upper limit values. Clinico-biological variables were analysed using the Mann-Whiney, Fisher's exact or Chi-square tests when appropriated.

Figure 1

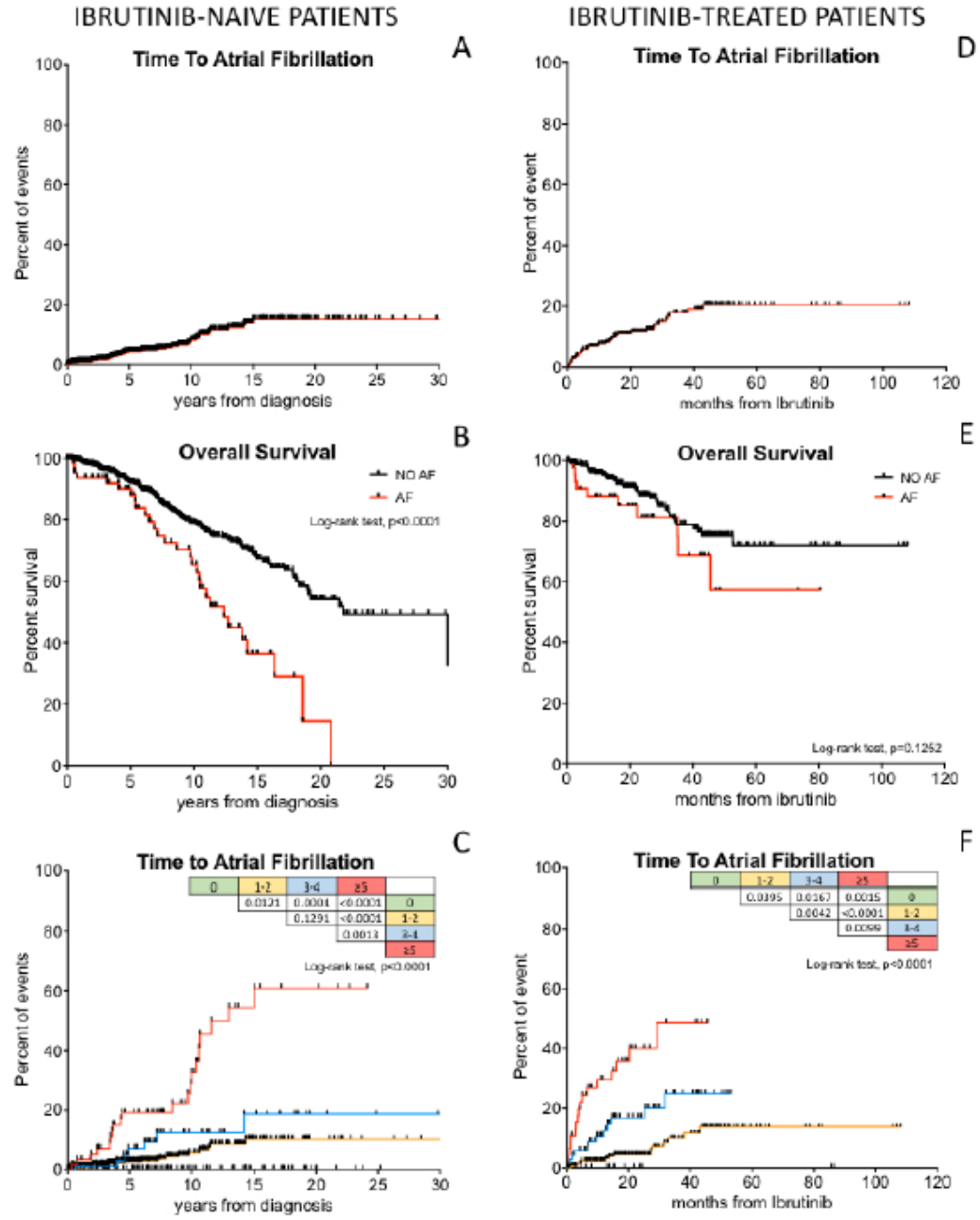

Figure 1. Kaplan-Meier curves of time to atrial fibrillation and overall survival. The left panels show the time to atrial fibrillation (A), overall survival (B) and time to atrial fibrillation according to our proposed scoring system (C) for the ibrutinib-naive patients from the Padua hospital. The right panels show the time to atrial fibrillation (D), overall survival (E) and time to atrial fibrillation according to our proposed scoring system (F) for the cohort of ibrutinib-treated patients.