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THE CARDIOVASCULAR IMPACT OF IBRUTINIB THERAPY

SUMMARY OF THE DOCTORAL THESIS

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INTRODUCTION

Cardiotoxicity induced by antineoplastic therapy has become a leading cause of morbidity and mortality among cancer survivors. [1][2][3] Adding the fact that cardiac pathology and cancers occupy leading places among the current world causes of morbidity and mortality [4][5][6][7][8], we can easily notice the medical and socio-economic importance, worldwide, of the research of these fields. This explains the extent that the field of cardio-oncology has taken in the last decade, although the term has been used since 1960. [9] However, despite the fact that cardiovascular diseases and neoplasias share a number of modifiable risk factors [10][11] and pathophysiological mechanisms [10][12][13], often coexisting in the same individual [14], cardiology and oncology are, most frequently, perceived as separate fields [15][5].

New therapies used in oncology and hematology have improved the prognosis of patients with malignancies.[16] In the last two decades, the development of antineoplastic therapies has been accelerated [17][11], including targeted medications [6][18] such as ibrutinib. This development, in addition to the undeniable benefits, also brought many unknowns, which require dedicated research. Ibrutinib, a discovery of the last decade, successfully used in certain types of malignant pathologies of B cells [19], brings with it a series of cardiovascular side effects not very clearly known and understood. Identifying them as early as possible is of great importance, being able, through the application of optimal management, to increase the quality of life and the prognosis of patients. [20][21] The initial definition of cardiotoxicity is based on the significant decrease in LVEF, classically evidenced in the case of anthracyclines and trastuzumab. [22]However, LVEF cannot identify cardiac damage quickly enough. [23] In addition, the complexity of cardiovascular complications of antineoplastic therapy (electrical abnormalities, cardiac dysfunction including subclinical damage, vascular toxicity – i.e. HTN, pulmonary hypertension –, thrombosis, myocardial ischemia, myocarditis, pericardial or valvular damage) extends beyond LVEF changes, other tools being needed to manage the broad potential for cardiovascular toxicity. [22] Revolutionary therapy with high efficiency in B-cell malignancies, first approved in 2013, ibrutinib, the first oral BTK inhibitor, still has adverse effects that cardiologists should also be aware of. [24] Among these, rhythm disorders, especially atrial fibrillation and hypertension are the most frequently mentioned. [25][26]

Although development efforts reflect the need and enthusiasm for cardio-oncology, this field is still in its infancy, with most recommendations and guidelines based on expert opinion or data from small studies. [27]

Starting from the review of the specialized literature and taking into account the feasibility of the evaluation in our clinic of patients treated with ibrutinib, we realized the opportunity constituted by starting a research project in this field, especially since in the country until the time of conducting this study no more a similar one was made. Thus, the Hematology departments of the Colentina Clinical Hospital and, to a lesser extent, the Colțea Clinical Hospital, provided patients receiving ibrutinib. In the Cardiology department of the Colentina Clinical Hospital, having the possibility of evaluating biomarkers such as high-sensitivity cardiac troponin, NTproBNP, echocardiography including advanced speckle-tracking techniques and equipment for 24 hours ambulatory monitoring of both blood pressure and electrocardiographic, I initiated this study.

Biomarkers and advanced echocardiographic techniques have been noted as sensitive tools for detecting subclinical cardiotoxicity. [28][29][30] Thus, we considered it important to evaluate the value of troponin and NTproBNP in the estimation of cardiac damage also in patients treated with ibrutinib. Furthermore, to date, there have been no published studies based on the determination of myocardial deformability in this population, although more and more data are beginning to emerge to emphasize the importance of trying to detect cardiotoxicity as early as possible using the speckle-tracking technique. [31]

I. GENERAL PART

The general part of the thesis, structured in three chapters, brings to the fore data obtained by studying the specialized literature. We have structured information related to the field of cardio-oncology, insisting on cardiotoxicity, the role of biomarkers and the use of the speckle-tracking technique. We also highlighted thesis-relevant aspects related to ibrutinib, starting from structure, pharmacodynamics and pharmacokinetics, mechanism of action, development and approval process, indications and known side effects, to reviewing the relationship of ibrutinib with the cardiovascular system, presenting pathophysiological links and mechanisms, communicated to date, of the most common cardiovascular adverse reactions of this new therapy.

The second part of the thesis, dedicated to **personal contributions**, mainly structures the results obtained.

II. PERSONAL CONTRIBUTIONS

HYPOTHESIS AND RESEARCH OBJECTIVES

The present study is designed to evaluate the **hypothesis** that ibrutinib can be related to the presence of clinical and especially subclinical cardiovascular damage.

The general objectives of the study are represented by:

- evaluation of the role of modern speckle-tracking imaging techniques in the detection of cardiotoxicity in patients treated with ibrutinib;
- identifying the link between changes in myocardial deformability in patients treated with ibrutinib and other factors:
    - hypertension;
    - the presence of arrhythmias;
    - the presence of changes in laboratory analyzes (such as anemia, increase in cardiac biomarkers (high-sensitivity cardiac troponin and NT-proBNP));
    - other echocardiographic parameters (example: LVEF, diastolic function);
- evaluation of other ibrutinib-induced echocardiographic changes;
- evaluation of the role of biomarkers - high-sensitivity cardiac troponin and NT-proBNP - in signaling cardiotoxicity induced by ibrutinib;
- evaluation of possible electrocardiographic changes induced by ibrutinib;
- evaluation of the association between arterial hypertension diagnosed by 24 hours ambulatory monitoring of blood pressure and the use of ibrutinib;
- identification of possible episodes of atrial fibrillation among patients treated with ibrutinib included in the study.

GENERAL MATERIALS AND METHODS

The study included 31 patients with hematological pathology under treatment with ibrutinib, taken from the Hematology section of the Colentina Clinical Hospital, according to the inclusion and exclusion criteria, in the period 2019-2020. Patients were evaluated at inclusion and 3 months apart, this interval being chosen following the literature review.

The small number of patients is due to the recruitment from a numerically limited background population: the average number of patients treated with ibrutinib is 30 per center (information obtained from coordinators of hematology departments in Bucharest). In 2019, there were approximately 700 patients nationwide receiving ibrutinib therapy (source: the manufacturing company). Unfortunately, there is no national registry for these patients.

Studies dedicated to ibrutinib, including multicenter randomized trials, have also involved relatively few patients. In the iLLUMINATE study, 113 patients were randomized to receive ibrutinib out of a total of 229 patients [32]. In the RESONATE study, 195 patients received ibrutinib [33]. In the RESONATE-2 study, the number of patients who received ibrutinib was 136 [34]. In iNNOVATE, the first Phase III study that led to FDA approval of ibrutinib in combination with other medication for Waldenström's macroglobulinemia, 75 patients received ibrutinib therapy [35]. A substudy of iNNOVATE, which was multicenter (19 centers across 7 countries), included 31 participants [36]. The HELIOS study, in the ibrutinib arm, included 289 patients [37].

Therefore, the present study presents **the experience of a single center** with patients undergoing ibrutinib therapy.

The patients were evaluated at the two time points through medical history, clinical examination, electrocardiogram, echocardiography, including speckle-tracking, ambulatory blood pressure monitoring (ABPM) for 24 hours, and 24-hour Holter monitoring. The echocardiographic measurements were performed using standardized methods.

The ultrasound parameters assessed included the dimensions of cardiac cavities, aorta, and inferior vena cava. Valvular morphology was examined, and any existing valvulopathies were quantified. The appearance of the pericardium was evaluated. Systolic functions of the left and right ventricles were assessed, as well as left ventricular diastolic function. Parietal kinetics were evaluated through both qualitative assessment and objective quantification using myocardial deformability parameters, utilizing speckle-tracking techniques.

To assess the systolic function of the left ventricle, the following parameters were quantified: shortening fraction; MAPSE (mitral annular plane systolic excursion); ejection fraction. Systolic function was also assessed by tissue Doppler imaging. The parameters obtained with pulsed tissue Doppler were recorded: the maximum systolic velocity, marked s, at the level of the septal and lateral mitral annulus, this being a good indicator of the global systolic function with independent prognostic value. [38]

Regarding the assessment of systolic function by newer techniques, we used the speckle-tracking technique, which performs the study of myocardial deformability. The methodology is based on frame-by-frame tracking of the direction and distance of movement of tissue markers, thus deriving data on myocardial velocities and deformation. This technique, being independent of the angle of incidence, allows the measurement of deformation at the level of all myocardial segments. [38] We used 2D speckle-tracking techniques.

We used the *Automated Function Imaging* (AFI) technique, in which, after calculating the longitudinal strain for each individual segment, the average for all segments can be calculated - global strain (*global longitudinal strain* - GLS), and based on the bull´s eye map we can appreciate, from the point of view of deformability, each myocardial segment.

The right ventricle was evaluated, apart from the dimensions, by TAPSE (tricuspid annular plane systolic excursion), being the most used method in practice due to the ease of evaluation and the prognostic information. The function of the right ventricle, due to its complex shape, unassimilable to any known geometric shape, is difficult to explore with the classic two-dimensional ultrasound.

To assess the diastolic function of the left ventricle, the following parameters were quantified: the maximum speed of early diastolic filling (E wave); maximum velocity of late diastolic filling by atrial contraction (A wave); E/A ratio; E-wave deceleration time (TDE); myocardial velocities recorded with the pulsed Doppler system adjusted for low velocities: septal and lateral S, e´, a´ waves and e´/a´ ratio; the E/e' ratio.

Laboratory analyzes were collected at each study visit. These included high-sensitivity cardiac troponin (hs-cTn), NT-proBNP, blood count, creatinine, TGO, TGP, blood glucose.

An Excel database was created, in which the obtained data were recorded. The data thus obtained were statistically processed. A licensed statistical data processing software was used.

The inclusion criteria in the study were: 1) Patients with hematological disease in therapy with ibrutinib; 2) Blood pressure values controlled at the time of the echocardiographic evaluation; 3) The patient's age must be greater than or equal to 18 years; 4) Signed informed consent obtained prior to study enrollment.

Exclusion criteria were: 1) Infections or fever at the time of echocardiographic evaluation; 2) Parallel participation in other non-observational studies; 3) Suboptimal echocardiographic window for calculating myocardial deformability parameters; 4) Known history of cardiac disease; 5) Lack of informed patient consent.

Statistical data analysis was performed using IBM SPSS Statistics 25 and Microsoft Office Excel/Word 2013. Quantitative variables were tested for distribution using the Shapiro-Wilk test and were expressed as means with standard deviations or medians with interpercentile ranges. Categorical variables were expressed in absolute form or percentages.

Quantitative independent variables with non-parametric distribution were tested using the Mann-Whitney U test, and Spearman's rho correlation coefficient was used for correlations between them.

Paired quantitative variables with parametric distribution were tested using the Paired Samples T-Test. Paired quantitative variables with non-parametric distribution were tested using the Related-Samples Wilcoxon Signed Rank Test.

Categorical variables were tested using the Fisher's Exact Test, and in the case of paired categorical variables, the McNemar test was used.

The main **limitation of this study**, which also reduces its statistical power, is the small number of patients included. This limitation is caused by multiple factors: the small background number of ibrutinib users in Romania, which is consistent with the overall low number of patients in studies involving ibrutinib. Therefore, recruitment was done from a numerically limited population (as detailed above), compounded by the pandemic context. As a result, patients with hematological disorders who were not infected with SARS-CoV-2 could no longer be evaluated at our hospital. This led to a reduction in the number of planned visits from three to two, which represents another limitation (short follow-up duration).

RESULTS

Clinical and laboratory data

The mean **age** of patients in the present study was 67.06 ± 10.38 years, which is consistent with the mean age of patients in established ibrutinib studies such as iNNOVATE, where the mean age was 67 years [39], RESONATE – 67 years [40], RESONATE-2 – 71 years [34], HELIOS – 64 years [37], iLLUMINATE – 70 years [32], Burger et al. in a study that included 259 patients - 73 years [41]. Also, the average age of diagnosis of chronic lymphatic leukemia, the most common pathology in our study and also the most common type of leukemia in adults [42], is 70 years [43].

In our study, we detected **atrial fibrillation** in 9.67% of patients (3 out of 31), 6.45% of them had the diagnosis because they benefited from 24hours Holter monitoring, practically active screening. All had silent episodes of atrial fibrillation, none describing symptoms during recording of the rhythm disorder. Atrial fibrillation is one of the most common side effects related to ibrutinib therapy.[44] Data from the literature provide similar percentages, atrial fibrillation occurring in 5-9% of patients during ibrutinib therapy [45], in the iLLUMINATE study the percentage was 6% [32], in RESONATE – 12% [33], the incidence going up to 16% in some studies [46]. The patients in our study who developed atrial fibrillation were all older than 65 years and two were hypertensive. Age over 65 years, hypertension, and ibrutinib therapy are significant risk factors for atrial fibrillation, with age and ibrutinib therapy being independent predictors of atrial fibrillation.[46]

Among the risk factors for the occurrence of atrial fibrillation is the **male gender** [47]. In our study, there was a definite dominance of the male sex (77.4%). In most studies with ibrutinib the number of men was also higher, but the difference was not as large, for example in the RESONATE study the percentage of men was 66.2% [40], in RESONATE-2 – 66, 2% men versus 33.8% women [34], iLLUMINATE – 59% men and 41% women [32].

Obesity is a cardiovascular risk factor and increases the risk of hypertension and atrial fibrillation [47][48]. In the present study, most patients are overweight - 77.41% having a BMI > 25 kg/m^2.

In the study group 35.2% of patients have **thrombocytopenia**, which is a predictor of bleeding risk in patients treated with ibrutinib for chronic lymphocytic leukemia [49]. As we discussed in the general part, the hemorrhagic risk is multifactorial in this population and, in case of the need for anticoagulant therapy (for example, the occurrence of atrial fibrillation secondary to ibrutinib therapy) or antiplatelet therapy, management becomes difficult for the clinician.

Additionally, 35.5% of the included patients have anemia, also increasing the hemorrhagic risk and placing additional demands on the cardiovascular system [50].

Anemia and thrombocytopenia are also consequences of haematological pathology, not only of therapy, in some studies [51] ibrutinib not being associated with a significantly higher risk of anaemia, thrombocytopenia or neutropenia.

A remarkable finding is represented by the significant differences between the two visits in the values of **cardiac biomarkers**. Thus, hs-cTn values from the first visit were lower compared to those from the second visit (p=0.019). Similarly, NTproBNP values from the first visit were lower compared to those from the second visit (p=0.030). Hs-cTn and NTproBNP are promising biomarkers for the identification of cardiotoxicity during neoplasia therapy, but currently the recommendations are based on expert opinion, and clinical studies are needed to optimally guide their use. [52] A recent meta-analysis including 61 studies with 5691 patients who received antineoplastic therapy [53] showed that both troponin and NTproBNP levels were increased in patients post-antineoplastic therapy. Moreover, troponin had a high negative predictive value (93%), and high level predicted left ventricular dysfunction. Thus, the meta-analysis concluded that troponin could be used as a screening test to identify patients who require cardio-oncological evaluation in dedicated departments, favoring the application of preventive measures. In contrast, NTproBNP did not consistently correlate with the prediction of left ventricular dysfunction. In the burgeoning field of cardio-oncology, biomarkers play an

essential role in risk assessment, diagnosis, monitoring of antineoplastic therapy and cardiotoxicity. [54][22][55][56][57][58][59]

Echocardiographic data

Regarding **LVEF**, there were no significant changes between the two evaluations, neither for the visually estimated value, nor for the biplane calculated value. LVEF was preserved (>50%) in all patients at both visits. These aspects are important, as they emphasize that the follow-up of cardiotoxicity only by LVEF is not very sensitive, nor does it allow its early detection, although biplane measured LVEF is the most used parameter for echocardiographic monitoring of left ventricular function [23]. In addition, LVEF measured using 2D biplane techniques has a temporal coefficient of variation of 7.4% [60] influenced by sonographer, geometric assumptions. We emphasized in the general part the importance of detecting cardiotoxicity as early as possible, LVEF not being an optimal parameter for this purpose.

Remarkable is the observation that the differences in **longitudinal global strain** values between the two visits were significant ($p<0.001$), the GLS values from visit 1 (-19 ± 2.53) being lower compared to the GLS values from visit 2 (-17.32 ± 2.5). Significant decrease in global longitudinal strain is common in chemotherapy patients. [1] In a 2018 study[1] no other echocardiographic parameter predicted the decrease in longitudinal global strain. The mechanism of the reduction of the global longitudinal strain could consist in the death of cardiomyocytes, included in the type I cardiotoxicity, classically described in the case of doxorubicin. [61]

As we have just pointed out, a decrease in global longitudinal strain is common among neoplastic patients and more importantly, most often, it is not accompanied by a decrease in LVEF. [1] Several theories have been proposed to explain the better sensitivity of myocardial strain than LVEF as a possible early predictor of cardiotoxicity. One of these is constituted by the idea that the suffering is mainly in different myocardial regions depending on the chemotherapy, thus certain myocardial segments are more affected than others, leading to the early modification of the GLS [62], the LVEF being maintained within normal limits by compensation dysfunction of some myocardial regions by unaffected myocardial segments [1]. Another explanation concerns the determination techniques of FEVS and global longitudinal strain. [1] LVEF measurement is indirect, assuming an approximation by tracing the endocardium [62][63] and varies over time depending on parameters such as heart rate, preload, etc. [64] The overall longitudinal strain can, on the other hand, be measured more precisely. [1]

The dimensions of the heart cavities did not change significantly between the two evaluations, except for the diameter of the right atrium, which increased significantly at the

second visit (p=0.025), thus the median from visit 1 was 38, and at visit 2 it was 40. This was also noted for the estimated systolic pressure in the pulmonary artery, the PAPs values from the first visit being much lower compared to the PAPs values from the second visit, the difference between the two visits being statistically significant (p=0.031). Up to this point, we have not identified in the literature a plausible explanation for the observed aspects.

We also observed that patients who had greater increases in right atrial mediolateral diameter (A4C) values at the second visit also more frequently had an associated greater increase in echocardiographically estimated pulmonary artery systolic pressure values at the second visit, this correlation being significant and highly positive ($p<0.001$, $R=0.712$).

Analyzing further, we noted that patients who had greater increases in **echocardiographically estimated pulmonary artery systolic pressure** values at the second visit also had a higher associated increase in atrial extrasystolic load values at the second visit (significant correlation and moderately positive ($p=0.048$, $R=0.399$)).

In a study published in 2018 in the American Journal of Cardiology, neither PAPS nor TAPSE, as a parameter of right ventricular function, predicted the reduction of global longitudinal strain. [1]

Regarding the **myocardial tissue velocities**, statistically significant differences were found in the case of the septal e´ wave and, consequently, also in the case of the average e´ wave. The differences in the septal e' wave values between the two visits were significant (p=0.017), the septal e' wave values from visit 1 (7.62 ± 2.43 cm/s) being lower compared to the septal e' wave values from visit 2 (7.95 ± 2.36 cm/s). Similarly, the mean e-wave values from visit 1 (8.45 ± 2.19 cm/s) were lower compared to the mean e-wave values from visit 2 (8.84 ± 2.14 cm/s), the difference having statistical significance (p= 0.029). The wave is recorded in protodiastole using tissue Doppler, it depends mainly on ventricular relaxation; when diastolic function is abnormal, the e' wave is relatively independent of preload. When diastolic function is normal, the e' wave increases with increasing filling pressures, so its utility in normal subjects is limited. The e' wave correlates with protodiastolic relaxation. [38] The normal value of the septal e´ wave is over 10 cm/s. [38] The increase in septal tissue velocity between visits is surprising, but without a clear explanation. The idea of a compensatory mechanism at the level of unaffected myocardial regions would be plausible. Nor do the data in the literature have very clear conclusions regarding the usefulness of diastolic function parameters in highlighting cardiotoxicity. Although diastolic dysfunction may reflect subclinical left ventricular dysfunction, it appears to be unable to predict cardiotoxicity, and the clinical significance remains unclear. In a study published in 2018 in the American Journal of

Cardiology [1] diastolic parameters such as E/A, TDE, e´ septal, E/e´ were not significant predictors for the reduction of global longitudinal strain.

ECG data

Regarding the data provided by the **electrocardiogram**, we found, in agreement with the specialized literature [65], that the differences in the **QTc interval** values between the two visits were not significant (p=0.274), the QTc values from visit 1 (432.13 ± 17.08 ms) being similar to the QTc values from visit 2 (430.97 ± 17.503 ms). We found the same thing for the **PR interval**.

Most studies show that ibrutinib does not prolong the QT interval. [66] There are also fewer studies that have found both measured and corrected QT shortening after exposure to ibrutinib, suggesting that this may be an electrophysiological mechanism involved in the generation of arrhythmias associated with this therapy. [67]

From the data provided by the **24 hours Holter monitoring**, it is worth emphasizing the significant difference (p=0.019) between the number of **atrial extrasystoles** and implicitly the difference in atrial extrasystolic load, between the two visits (see tables 6.30, 6.31 and figures 6.25, 6.26). We could consider that the increasing number of supraventricular extrasystoles signal the arrhythmic potential of ibrutinib and precede the onset of a sustained rhythm disorder, including atrial fibrillation, which should, in practice, intensify screening for their detection. In a study published in 2019 that excluded patients with a history of arrhythmias, ibrutinib was shown to be an independent risk factor for the development of atrial arrhythmias. [68] In the literature, there are mainly data on atrial arrhythmias such as atrial fibrillation/atrial flutter associated with ibrutinib therapy and less data on atrial or ventricular extrasystolic load.

In our study, the differences in the number of atrial extrasystoles reported in patients with or without ECG-diagnosed left atrial dilatation were not significant (p=0.251). A pertinent explanation for the lack of correlation of these elements, named in other words: left atrial remodeling – intraatrial ectopic foci, could be represented by the lack of statistical power of our study, generated by the small number of analyzed patients.

In a retrospective study of 183 patients [69] left atrial loading identified on the electrocardiogram was a significant predictor of atrial fibrillation in patients receiving ibrutinib, being a marker with moderate specificity and sensitivity that can identify patients at increased risk for this toxicity.

In contrast, by 24 hours Holter monitoring, we found no significant differences between the two visits regarding the number of ventricular extrasystoles or the number of ventricular or supraventricular tachycardias. However, ibrutinib, an arrhythmogenic molecule with not very

clearly understood mechanisms, seems to be also responsible for ventricular arrhythmias, but to a lesser extent, or at least less frequently reported. As we have shown in the general part there are few case reports with ventricular arrhythmias caused by ibrutinib (chapter Adverse reactions ibrutinib). In ibrutinib trials, 10 cases of sudden cardiac death (SCD) were identified in approximately 1000 enrolled patients, thus a significantly higher incidence compared to the SCD rate in the population over 65 years of age. [70]

In a mouse study, ibrutinib was shown to cause myocardial fibrosis and collagen deposition. [71] Myocardial fibrosis plays an essential role in the constitution of the arrhythmic substrate. [72] Also, in the same study [71] it was shown that ibrutinib causes ultrastructural changes in the mitochondria of atrial myocytes, with the evidence of mitochondrial edema and implicitly the deformation of the mitochondria and the rupture of the mitochondrial cristae.

Data provided by 24h ambulatory blood pressure monitoring

24 hours ambulatory monitoring of blood pressure (BP) showed no significant differences between the two visits. Mean daytime BP was approximately 132/78 mmHg and mean nighttime BP was approximately 125/71 mmHg.

Of the patients evaluated by 24hours ambulatory monitoring of BP, 19% had thus established the diagnosis of HTN at the first visit, respectively 67.74% at the second visit. 32.25% of the included patients had a history of hypertension and 29.03% were taking antihypertensive treatment, the percentage of those treated rose to 35.48% at the second visit. The percentage of hypertensive patients in our study is close to that reported in oncology registries, with HTN being the most common cardiovascular comorbidity reported in these registries, with a prevalence of 37%. [73] Of the "non-hypertensives", only 50% had a blood pressure profile of dipper type at the first visit, at the second visit two thirds had a blood pressure profile of non-dipper type, the term dipper meaning the decrease of nocturnal BP by >10% from average diurnal BP [48]. However, dipper status is often highly variable from day to day, being hardly reproducible [74]. Nocturnal BP is a better predictor for prognosis than diurnal BP, patients with a decrease in nocturnal BP <10% of diurnal BP (non-dipper profile) have an increased cardiovascular risk [75], moreover, no decrease or even an increase in nocturnal BP (reverse-dipper) generates a substantial increase in risk [76].

In our study, preexisting hypertension did not significantly influence the frequency of left atrial load at the second visit, which is most likely caused by the small number of patients analyzed in our study.

The increased incidence of hypertension in the present study population is justified by the association of two important risk factors: advanced age and ibrutinib use. HTN, in turn, is not

only a risk factor for atrial fibrillation, but also for ischemic or hemorrhagic stroke [77][78], and ibrutinib and the hematological pathology for which it is used, through platelet damage and substrate generation arrhythmic, they close a vicious circle of hemorrhagic and arrhythmic risks.

Data provided by comparative analysis of various parameters

We found that there were no statistically significant differences between the two visits in relation to: gender distribution, alcohol consumption or pre-existence of arterial hypertension, regarding Ths troponin values, NTproBNP, right atrial dimensions, $_S$PAP, wave values e´ septal and average, of the global longitudinal strain or of the number of atrial extrasystoles, respectively the atrial extrasystolic load. In contrast, when comparing the differences in hs-cTn between visits with the presence of smoking we observed that the differences were statistically significant (p=0.026), with non-smokers having, unexpectedly, higher increases in troponin compared to smokers. We have not identified a clear explanation for this situation, especially since the average age is similar between the two groups (66.8 years - smokers vs. 67.1 years - non-smokers), and the comorbidities do not differ significantly between the groups. On the other hand, all smokers are men and have a BMI > 25 kg/m^2 (in the group of smokers the average BMI was 27.82 kg/m^2, and in the group of non-smokers it was 26.94 kg/m^2), practically being associated 3 cardiovascular risk factors.

Correlations

Analyzing various potential correlations, we observed that in the studied group, patients who had **greater increases in hs-cTn** at the second visit also more frequently had associated a **greater increase in the global longitudinal strain values of the left ventricle** at the second visit, in other words they had a greater decrease in myocardial deformability, the correlation being significant and moderately positive (p=0.020, R=0.417). In contrast, in the case of NTproBNP, the changes in the biomarker values between the two visits were not significantly associated with the changes in the global longitudinal strain values of the left ventricle. As mentioned above, NTproBNP does not appear to correlate with the prediction of left ventricular dysfunction in patients receiving antineoplastic therapy, unlike troponin.

Troponin and global longitudinal strain predict the development of cardiotoxicity in patients treated with anthracyclines and trastuzumab. [62] In the same study [62] cardiotoxicity was not predicted by early changes in LVEF or NTproBNP level, which is in agreement with our data.

Another aspect observed, also important, is that, in the studied group, patients who had **greater increases in hs c-Tn** at the second visit had, more frequently associated, a **greater**

increase in atrial extrasystolic load recorded by 24 hours Holter monitoring at the second visit, this correlation being significant and moderately positive (p=0.023, R=0.414). Furthermore, in this case, the observation also holds for NTproBNP. Thus, patients who had **greater increases in NTproBNP** at the second visit also had, more frequently associated, a **greater increase in the number of atrial extrasystoles** recorded by 24 hours Holter monitoring at the second visit and implicitly in the atrial extrasystolic load . These correlations were statistically significant (p=0.004, respectively p=0.011). Both changes (both the increase in cardiac biomarkers and the increased number of extrasystoles) translate cardiac distress and myocardial remodeling, including electrical, their temporal sequence cannot be delimited, being rather intricate.

We also found that patients who were diagnosed with HTN based on 24 hours ambulatory blood pressure monitoring had significantly higher increases in global longitudinal strain of the left ventricle at the second visit compared to patients without HTN (p=0.003). So, hypertensive patients experienced a decrease in longitudinal myocardial deformability. Myocardial systolic deformability is dependent on filling pressures, decreasing under conditions of increased afterload. [79] Myocardial remodeling and altered ventricular filling conditions in hypertensive patients influence myocardial strain. [79]

On the other hand, age, the presence of anemia or atrial extrasystolic load did not significantly change, in the studied group, the evolution of the longitudinal global strain values of the left ventricle between visits. Regarding age, it was found, in the healthy population, that the global longitudinal strain is lower in the elderly compared to the young, but remains within normal limits. [80] With regard to anemia, the data agree with the literature, thus in a study published in 2019 in the American Journal of Cardiology conducted on patients with heart failure with preserved LVEF, it was found that anemia was not associated with markers of intrinsic myocardial dysfunction, of the foreign type of the myocardial or of the type of myocardial velocities e´ lateral, e´ septal [81]. Conversely, anemia was associated with markers of diastolic dysfunction – volume-dependent markers (preload), including E/A, E/e' ratios, and with increased right heart pressure such as right atrial pressure and PAPS. In our study, however, we did not identify correlations between anemia and E/A, E/e´ ratios, right atrial diameter, or ultrasound-estimated pulmonary artery systolic pressure.

CONCLUSIONS AND PERSONAL CONTRIBUTIONS

The data from the present study provide information about the characteristics of the patients under treatment with ibrutinib, most of them taken from the Hematology department of the Colentina Clinical Hospital, about the cardiac damage among them, including the occurrence of rhythm disorders (atrial fibrillation, atrial or ventricular extrasystoles, supraventricular tachycardias or ventricular), of arterial hypertension and the reduction of myocardial deformability expressed by the global longitudinal strain (GLS) value.

The novelty of the study lies in the assessment of myocardial deformability in patients receiving ibrutinib. Additionally, in our study, patients underwent ABPM/24h and 24-hour Holter monitoring. Moreover, the comprehensive imaging, clinical, and laboratory evaluation has not been previously addressed in a similar manner, to the best of our knowledge. Until now, no study has been reported in Romania encompassing the evaluations presented in our study.

We have set out below the **conclusions** of the study carried out involving **personal contributions**. The **conclusions** of our study are as follows:

1) The evaluation of myocardial strain in patients undergoing ibrutinib therapy is useful in early identification of cardiotoxicity, surpassing the sensitivity and specificity of left ventricular ejection fraction (LVEF). (subchapters 6.2.2, 6.3, 6.4)
2) Monitoring ibrutinib-induced cardiotoxicity solely through LVEF is not highly sensitive and does not allow for early detection. LVEF is not an optimal parameter for this purpose. (subchapter 6.3)
3) The correlation of global longitudinal strain of the left ventricle with cardiac biomarkers, especially high-sensitivity cardiac troponin, increases the power to identify subclinical myocardial impairment in patients treated with ibrutinib. (subchapter 6.3)
4) Increased high-sensitivity cardiac troponin correlates with decreased myocardial deformability, being a useful predictor of left ventricular dysfunction in patients receiving ibrutinib therapy. Conversely, increased NT-proBNP does not appear to correlate with the prediction of left ventricular dysfunction in patients receiving antineoplastic therapy. (subchapter 6.3)
5) The increase in cardiac biomarkers (troponin, NT-proBNP) correlated with the increase in atrial extrasystolic load in the population receiving ibrutinib. (subchapter 6.3)
6) Active screening through electrocardiogram and/or 24-hour Holter monitoring is necessary for patients undergoing ibrutinib treatment to identify rhythm disturbances, which are often silent. As a result, we detected atrial fibrillation in 9.67% of the patients in the study, with all recorded episodes being asymptomatic. (subchapters 6.2.3, 6.2.4, 6.4, 6.5)

7) The changes recorded through 24-hour electrocardiographic monitoring, such as an increase in extrasystolic load, should suggest possible ibrutinib-induced myocardial toxicity and prompt further evaluation, including the measurement of cardiac biomarkers and assessment of echocardiography, including myocardial deformability. (subchapters 6.2.4, 6.4)
8) 24h ambulatory blood pressure monitoring of patients treated with ibrutinib is necessary, significantly increasing the diagnosis of hypertension in this population and, consequently, optimizing their therapeutic management. (subchapters 6.2.5, 6.4)
9) Myocardial deformability assessed at the second visit decreased significantly more in patients diagnosed with HTN by 24h ambulatory blood pressure monitoring compared to patients without HTN. Blood pressure increases in the ibrutinib population should also prompt echocardiographic evaluation, including speckle-tracking. (subchapters 6.2.5, 6.3, 6.4)
10) Ibrutinib does not seem to modify the QTc and PR intervals. In our study, we did not observe significant changes in these values between visits, which is consistent with the data reported in the literature. (subchapters 6.2.3, 6.4)
11) At the second evaluation, we observed an increase in the size of the right atrium and an increase in estimated echocardiographic pulmonary arterial pressure. Additionally, patients who had larger increases in pulmonary arterial systolic pressure values at the second visit were more frequently associated with a greater increase in atrial extrasystolic load values. (subchapters 6.2.2, 6.3, 6.4)
12) Surprisingly, we observed an increase in septal myocardial tissue velocities (septal e' wave) between visits, with a possible plausible explanation being the compensatory mechanism in unaffected myocardial regions. Although diastolic dysfunction may reflect subclinical left ventricular dysfunction, it seems that it cannot predict cardiotoxicity, and the clinical significance remains unclear. (subchapters 6.2.2, 6.4)
13) Measurement of cardiac biomarkers (high-sensitivity cardiac troponin, NT-proBNP) and the use of 24-hour ambulatory blood pressure and electrocardiographic monitoring, along with echocardiography including speckle-tracking and correlation of the obtained data, are valuable in identifying ibrutinib-induced cardiotoxicity. (subchapters 6.2.1, 6.2.2, 6.2.3, 6.2.4, 6.2.5, 6.3, 6.4)

The interdisciplinary character of the conducted research emerges from the usefulness of the information obtained both for cardiologists, hematologists, oncologists, as well as for specialists in internal medicine, family medicine and even laboratory medicine, who

contribute to the care of these patients.[82] Collaboration between cardiologists and oncologists/hematologists is of real importance.[28] A 2017 study demonstrated significantly reduced mortality in patients with hematologic malignancies who received multidisciplinary team evaluation prior to initiation of treatment compared to those who did not.[83] Cardio-oncology is located at the intersection of oncology/hematology with cardiology, focusing on the reduction and management of pre-existing or emerging cardiovascular disease in neoplastic patients.[84][85][86] A key goal of cardio-oncology is to enable optimal anticancer therapy assuming the lowest cardiovascular risk, which requires experts in the field, specific skills and dedicated training.[87] Prevention in cardio-oncology appears of real importance [88], especially as the number of survivors of malignancies in the United States is estimated to increase from ~17 million in 2019 to ~22 million in 2030 [89].

The current pandemic context, which has partially affected the completion of this study, exposes cardio-oncology patients to an increased risk not only through the direct probability of SARS-CoV-2 infection but also through the disruption of their care routine [90]. Adapted solutions and marked flexibility in dedicated centers are urgently needed.

Regarding the **perspective directions**, we consider the aspects presented in the following lines to be desirable.

The establishment of a cardio-oncology center, similar to existing models abroad, where patients receiving antineoplastic therapies can be evaluated by highly qualified multidisciplinary teams, is a desirable goal. This would ensure that patients receiving ibrutinib, among others, receive appropriate cardiovascular evaluations. The benefits would be bilateral, benefiting both the patients and the healthcare professionals/researchers. Referrals from multiple centers would lead to the evaluation of a significantly larger number of patients. This would increase the level of knowledge and enable studies to be conducted on larger cohorts, with better integration of information.

It is desirable for patients receiving ibrutinib treatment to undergo echocardiographic evaluation, ideally using techniques such as speckle-tracking and 3D imaging, both before initiating therapy and subsequently at predefined intervals based on the observation of changes. The use of left atrial strain would be helpful in predicting the occurrence of atrial fibrillation. Additionally, 24h ambulatory monitoring of blood pressure and ECG, and periodic measurements of cardiac biomarkers would contribute to optimized management of patients receiving ibrutinib. In order to maintain a favorable prognosis for oncology patients, cardiotoxicity should be prevented or, at the very least, detected early and treated appropriately.

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