Comprehensive cardiac evaluation reveals no increase in ventricular arrhythmias in patients on chronic ibrutinib therapy: a study of KroHem, the Croatian cooperative group for hematologic diseases

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Targeted NGS Panel. Whereas the clinical significance of some mutations is currently uncertain, further research using NGS technology is required.

Chronic lymphocytic leukemia and related disorders - Clinical

PB1492 CLINICAL FEATURES OF LARGE GRANULAR LYMPHOCYTIC LEUKEMIA-ASSOCIATED PURE RED CELL APLASIA: RESULTS FROM A SINGLE CENTER IN CHINA

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Background: Large granular lymphocyte leukemia (LGLL)-associated pure red cell aplasia (PRCA) is a rare lymphoproliferative disorder. Only a few case series have been reported in the literature. so that the features and optimal treatment of the disease remains unclear.
Aims: We conducted this retrospective study to assess clinical features, immunological profiles and the outcome of treatment in patients with LGLL-associated PRCA.
Methods: A cohort of 20 patients with LGLL-associated PRCA who referred to our hospital from January 2013 to April 2020 was reviewed.
Results: The clinical characteristics of 20 patients included in this study showed that no differences were evident based on sex. The median age of the patients was 50 years old (range, 28-76 years). Splenomegaly was observed in 45% of cases, most of which were characterized by mild to moderate enlargement. By contrast, hepatomegaly was rare (10%). Our study identified increased percentage and absolute number of $CD3^+CD8^+$ T cells, meanwhile decreased $CD3^+CD4^+$ T cells, $CD3^-CD16/CD56^+$ NK, $CD19^+$ B cells and CD4/CD8 ratio (Table 1). For treatment (Table 1), cyclosporine A (CSA) in combination with methylprednisolone (MP) was administered in 6 patients, with an complete and partial remission (CR+PR) of 50.0% (3/6). A novel immunosuppressive strategy of cyclosporine (CSA), low dose methylprednisolone (MP) and danazol(DNZ), which we named CMD regimen, was administrated orally with an initial dose of CSA 3mg/kg/day, MP 0.25–0.5 mg/kg/day, and DNZ 5.0-10.0 mg/kg daily as first-line therapy for 13 patients, of which ten responded positively(76.9%). One patient received antithymocyte globulin (ATG), resulting in no response (NR). Among the three patients who failed to respond and two relapse to first-line therapy of CSA and MP, four patients received the second-line therapy of CMD regimen, with an CR+PR of 60%. Another patient received ATG, and achieved complete remission (CR). Among the three patients who failed to respond and two relapse to first-line therapy of CMD regimen, three patient responded to the second-line therapy of CMD regimen plus methotrexate (MTX). Adverse events were uncommon, one patient had impairment of liver function with transaminase values up to 110 U/L.

Table 1 Immunological profiles and response to treatment of all patients

Immunological profiles (N=20)	Min	Max	Mean	SD	Reference range	Low ,N	Normal ,N	High ,N
$CD3^+T$(%)	85.3	98.5	94.2	3.4	56-86	0	1	19
$CD3^+CD4^+T$(%)	15.3	51.0	30.3	10.7	33-58	12	8	0
$CD3^+CD8^+T$(%)	22.4	80.5	57.2	15.4	13-39	0	1	19
CD4/CD8 ratio	0.2	1.3	0.6	0.4				
$CD3^-CD16/CD56^+$ NK(%)	0	6.4	1.7	1.9	5-26	18	2	0
$CD19^+B$(%)	0.6	9.2	2.6	2.6	5-22	17	3	0

Treatment	First-line therapy, n(%)			Second-line therapy, n(%)	
	N	CR+PR(%)	Relapse	N	CR+PR(%)
CSA+MP	6	2+1 (50.0%)	2 (66.7%)		
ATG	1	0+0 (0%)		1	1+0(100.0%)
CSA+MP+DNZ	13	7+3 (76.9%)	2(20.0%)	5	2+1(60.0%)
CSA+MP+DNZ+MTX	0			5	2+1(60.0%)

CsA cyclosporine A; MP methylprednisolone; ATG antithymocyte globulin; DNZ danazol; MTX methotrexate; CR complete remission; PR partial remission; NR no response;

Summary/Conclusion: This study provides new information regarding the clinical features and therapeutic strategies for LGLL-associated PRCA, which demonstrated that the CMD regimen could be a promising strategy for patients with LGLL-associated PRCA.The multiple-center clinical trial need to initiate to validate this conclusion.

PB1493 A RETROSPECTIVE ANALYSIS OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) TREATED WITH VENETOCLAX IN THE REAL-LIFE SETTING IN SPAIN (VENARES)

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Background: Pivotal clinical trials have shown Venetoclax (Ven; BCL inhibitor) good efficacy and safety profile. Studies in real life setting are limited as Ven is commercially available in Spain since April 2018.
Aims: To evaluate the effectiveness of Ven in adult CLL pts by the overall response rate (ORR) at 9 months (mo) after the first Ven dose administration, as assessed by the treating physician.
Methods: This is a Spanish non-interventional, retrospective, national, multicenter, post-marketing, observational study. Eligible subjects were adult pts with CLL who initiated Ven at least 9 mo before inclusion. Subjects in Early Access Program from Jan 2017 were included.
Data from approximately 100 pts is planned to be collected from 30 Spanish sites. Data of pts are retrospectively reviewed until the date of last follow-up or death.
Results: 48 pts were included in the interim study: 32 pts (66.7%) were male, the median age was 74.5 years (67.5-78), pts had received a median of 4 prior lines of therapy (range 1-10 lines). 15 pts had unmutated IGHV (88%), 10 pts (33.3%) had del(17p), 10 pts (33.3%) had TP53 mut. In 42 pts, median time from CLL diagnosis to Ven initiation was 78.5 m (38-125). 81.2% of pts received Ven monotherapy, 4.2% combined with rituximab, 2% with obinutuzumab,12.5% with other agents. Objective response was evaluated in 23/39 pts treated with Ven monotherapy.
48 pts (100.0%)had dose modifications, 19 (39.6%), dose interruptions, 19 (39.6%) discontinued Ven. 26 (54.2%) had TLS greater risk before Ven initiation, 22 pts were hospitalized during ramp-up.
14pts (29.2%) presented at least 1 SAE, 10 (20.8%) presented at least 1 SAE related to Ven. 6 pts (12.5%) presented 1 AE related to Ven that led to drug withdrawal. Percentages of Specific AEs were neutropenia (43.7%), febrile neutropenia (12.5%), serious infection (18.8%), TLS in 6.3% (2 laboratory,1 clinical) and Richter transformation (RT) (6.3%). Related to Ven were 4 febrile neutropenia (8.3%) and 1 lab TLS(2.1%).

Table: Outcomes with Venetoclax monotherapy	
Patients, n	39
Overall response rate in evaluable pts (23)	
CR/Cri	8 (34.8%)
PR/nPR	9 (39.1%)
ORR	17 (73.9%)
PFS est 24 mo	75.9% (56.2-87.6)
uMRD ($<10^{-4}$) in assessed pts, (%,n)	22.2% (2/9)

Summary/Conclusion: This preliminary effectiveness data suggest overall outcomes are similar to those in the pivotal clinical trials. Safety assessment show AEs reported were consistent with the safety profile seen in prior VEN studies and did not reveal unexpected AEs.

PB1494 COMPREHENSIVE CARDIAC EVALUATION REVEALS NO INCREASE IN VENTRICULAR ARRHYTHMIAS IN PATIENTS ON CHRONIC IBRUTINIB THERAPY – A STUDY OF KROHEM, THE CROATIAN COOPERATIVE GROUP FOR HEMATOLOGIC DISEASES

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Background: Ibrutinib is increasingly used for treatment of various B-cell malignancies. It's generally well tolerated, but has cardiovascular side-effect including hypertension and arrhythmias, most frequently atrial fibrillation (AFib). Data on the dynamics of frequency and severity of arrhythmias in patients on chronic ibrutinib treatment are lacking.
Aims: We initiated this prospective study to determine the impact of chronic ibrutinib therapy on incidence of supraventricular (SPB) and ventricular premature beats (VPB).
Methods: This was a multicentre, prospective, observational cohort study. Consecutive patients with hematologic malignancies starting ibrutinib therapy and without structural heart disease and clinically significant arrhythmias were included in the study. Cardiologic work-up included echocardiography and 24h-Holter-ECG. Diagnostic assessment was carried out before and repeated at 3, 6 and 12 months after the introduction of ibrutinib therapy. Primary endpoint was the number of VPBs on 24h-Holter-ECG; secondary endpoints were: number of SPBs on 24h-Holter-ECG, systolic left ventricular function, occurrence of AFib and newly diagnosed or worsened hypertension.
Results: 35 patients recruited from 4 hospitals were included in the study during 2019 and 2020 (Table 1). The most common indication for treatment was chronic lymphocytic leukaemia in 31 (89%) patients. Median age was 66 years (range 58-73), 54% were female. The most prevalent cardiovascular comorbidity was hypertension (45%), followed by smoking (29%). The remaining risk factors, including diabetes mellitus, stroke and coronary artery disease had a prevalence of <10%. Mean left ventricle ejection fraction was 60%, left atrial diameter 40±4 mm and volume 53±7 mL.After a median follow-up of 6 months, there was no significant increase in the number of VPBs (428±320 vs. 170±110, p=.19) or SPBs (245±104 vs. 532±305, p=.09). Hypertension was newly diagnosed or worsened in 8 patients (23%), and 2 patients developed paroxysmal AFib (6%). Ibrutinib was temporarily discontinued or its dose was adjusted in 3 patients due to non-cardiovascular side-effects.

Table 1. Baseline characteristics

	Total (N= 35)
Demographics	
Age (years)	66 (58-73)
Male sex (% (n))	46 (16)
BMI (kg/m^2)	27.3 ± 4.5
History (% (n))	
Hypertension	46 (16)
Diabetes mellitus	20 (7)
Hyperlipidaemia	23 (8)
Smoking	29 (10)
Stroke / TIA	0
Coronary artery disease	6 (2)
Chronic kidney disease	14 (5)
COPD/Asthma	6 (2)
CHA_2DS_2VASc score	2.35 ± 1.5
HAS BLED score	0.3 ± 0.45
Hemato-oncologic disease	
Chronic lymphocytic leukemia	88 (31)
Waldenstrom macroglobulinemia	6 (2)
Mantle-cell lymphoma	6 (2)
Echocardiography	
LVED diameter (mm)	47 ± 3
LA diameter (in PLAX) (mm)	40 ± 4
LA volume (mL)	53 ± 7
LVEF (%)	60 ± 3
TAPSE (mm)	21 ± 2
TAP (mmHg)	20 ± 2
Electrocardiogram	
Heart frequency	78 (72-85)
Sinus rhythm (yes/no)	100 (35)
Atrial premature beats	36 (7-141)
Ventricular premature beats	9 (2-49)

Summary/Conclusion: Prolonged treatment with ibrutinib had no significant impact on number of VPBs or SPBs. Our study suggests that ibrutinib does not significantly increase the propensity to develop dangerous cardiac arrhythmias in patients who do not have clinically important structural heart disease or arrhythmias prior to treatment start and stresses the importance of hypertension control in this group of patients.

PB1495 PROGNOSTIC VALUE OF IGHV MUTATIONAL STATE AT DIAGNOSIS FOR PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: Chronic lymphocytic leukemia (CLL) is a pathology with a variable clinical evolution; some patients remain indolent for many years while others require treatment, including shortly after diagnosis. Although molecular and genetic markers with prognostic value have been described, the current International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines only recommends their analysis prior to commencing treatment.
Aims: In this retrospective study, we analyzed the prognostic impact of molecular and genetic markers on CLL patients at diagnosis.
Methods: A consecutive series of 217 patients with CLL diagnosed in our hospital between 2008 and 2018 was analyzed. Clinical, molecular (*IGHV* and *TP53*) and cytogenetic data were collected at diagnosis.
Results: Our series confirmed the prognostic value of the CLL-IPI index for OS (p=0.003, Log-Rank test) and time to first treatment (TFT, p<0.001). In accordance with previously published results, Kaplan-Meier survival analyses identified an association between *IGHV* unmutated (p<0.022) (Figure 1**A** and **1B**) and shorter OS and TFT (p≤0.001). The variables age >65 years (p<0.001), β_2-microglobulin >3.5 mg/dL (p<0.001) and advanced Binet/Rai clinical stage (p=0.001) were also associated with shorter OS and TFT, while the presence of mutation/deletion of *TP53* (p=0.001) and deletion of 11q (p<0.001) were associated with shorter TFT. Unmutated *IGHV,* advanced clinical stage and age (albeit marginally) also showed independent prognostic value for OS as determined by multivariate analysis (**Table 1**, p=0.01, 0.033, and 0.072 respectively). For TFT, only unmutated *IGHV* and clinical stage (albeit marginally) had prognostic impact (p=0.001 and 0.081, respectively). Importantly, when only patients in the early stages were selected (RAI 0-2/ BINET A), *IGHV* mutation maintained prognostic value for both OS and TFT in the multivariate analysis (OS: OR 6.16, p=0.01/OR 5.96, p=0.009; TFT: OR 13.58, p=0.001/OR 14.08, p=0.001) and Kaplan-Meier survival analyses (OS: p=0.013, TFT: p<0.001) (Figure 1**C** and **1D**). The loss of prognostic value of β_2-microglobulin levels might be explained by the statistically significant association observed in our series between unmutated *IGHV* and β_2-microglobulin levels > 3.5 mg/dL (p = 0.002, Pearson's χ^2) as well as advanced age (p = 0.024, Pearson's χ^2). Chromosomal alterations, such as deletion/mutation of *TP53* and deletion of 11q, were not included in the multivariate analysis due to their low incidence in our series. A larger series would be required to evaluate their prognostic impact.

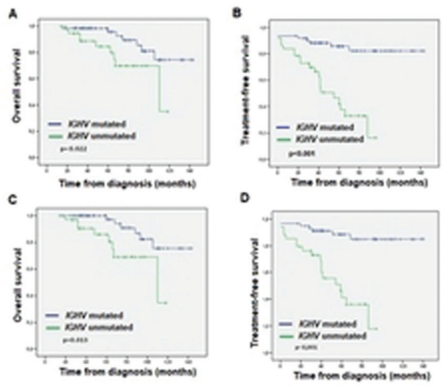

Figure 1. Kaplan-Meier survival curves according to *IGHV* mutational state. **A)** Overall survival (OS) in the whole series, **B)** Time to first treatment (TFT) in the whole series, **C)** OS in RAI stages 0-2, **D)** TFT in RAI stages 0-2.

Summary/Conclusion: *IGHV* mutational state was the only prognostic marker to have independent prognostic value for both OS and TFT, for the whole series as well as patients in the early stages. Our results indicate that the determination of *IGHV* mutational state at diagnosis informs the risk stratification of patients with CLL.