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Comparison of ibrutinib and idelalisib plus rituximab in real-life relapsed/resistant chronic lymphocytic leukemia cases

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Novelty Statements: The lack of phase III randomized trials leaves the queries on the choice of the most appropriate BCRi for R/R-CLL patients unresolved. The efficacy of ibrutinib vs idelalisib plus rituximab in terms of OS was compared in this real-life study. The results suggest the superiority of ibrutinib over idelalisib plus rituximab, independently of a series of well-known confounders, although the influence of potential residual confounding factors cannot be completely excluded. The retrospective nature of the study design poses some limits to the interpretation, even though the analyses are adjusted for baseline and biological characteristics. This information may be of help for the daily clinical practice.

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Abstract

Objectives: To compare the capacity of ibrutinib (IB) and idelalisib-rituximab (IDELA-R) of prolonging overall survival (OS) as in CLL patients, previously treated with chemotherapy only.

Methods: A real-life cohort of 675 cases has been identified and investigated in the database of the groups participating in the study.

Results: At an unadjusted univariate analysis, a significant death risk reduction was observed favoring IB (IDELA-R vs IB HR = 0.5, 95% CI = 0.36-0.71) although with some limitations due to the non-randomized and retrospective nature of the study and to the lower number of patients in the IDELA-R group (112 cases) related to the current prescribing practice. To overcome the potential problem of confounding by indication, we adjusted the association between the type of therapy and mortality for all variables significantly associated with OS at Cox univariate analysis. Furthermore, those variables, differently distributed between the two study groups, were introduced into the multivariate Cox model to improve the effectiveness of the analysis. By introducing all these variables into the multiple Cox regression model, we confirmed the protective effect of IB vs IDELA-R (HR = 0.67, 95% CI = 0.45-0.98, $P = .04$) independent of potential confounders.

Conclusions: Although our analysis presents some constraints, that is, the unavailability of additional potential confounders, and the retrospective nature of the study, this observation may be of help for the daily clinical practice, particularly in the absence of randomized trials comparing the two schedules.

KEYWORDS
chronic lymphocytic leukemia, ibrutinib, idelalisib, therapy

1 | INTRODUCTION

The treatment algorithm for chronic lymphocytic leukemia (CLL) is rapidly developing, with multiple new drugs being recently approved, including B-cell receptor signaling inhibitors (BCRi), that is, ibrutinib (IB),[1] idelalisib (IDELA),[2] and the BCL-2 inhibitor venetoclax.[3] These novel agents have entered into the CLL therapeutic armamentarium to substitute for or to integrate the conventional chemo-immunotherapy regimens. This is true especially for the patients with adverse cytogenetic or molecular features such as 17p13.1 deletions [del(17p)] and/or *TP53* mutations (*TP53*mut), or in the relapsing/resistant (R/R) CLL setting.[4-6] In connection with this, the

National Comprehensive Cancer Network (NCCN) suggests IB over IDELA plus rituximab (IDELA-R) as the preferred option,[7] while the European Society of Medical Oncology (ESMO) recommends IB or IDELA-R in the R/R setting.[8] However, the lack of phase III randomized trials, which unquestionably represents the optimal approach to generate clinical evidence, leaves unresolved queries on the most appropriate BCRi choice for R/R-CLL patients. Thus, despite some well-known limitations and susceptibility to bias, real-life evidence[9] is being progressively exploited in order to address the above-mentioned unanswered issue.[10,11]

In order to maximize the information, potentially provided by the real-life evidence, it is important to have an estimate of the value of all of the potential clinical, molecular, and cellular risk factors, given that these risk factors bear considerable relevance for a fair comparison between treatment groups, that could not obviously be randomized at the study start. CLL-IPI, the prognostic value of which was proven in patients treated with chemo-immunotherapy,[12] suffers from noticeable limitations when BCRi are utilized.[13] Recently, the assessment of the value of potential risk factors for overall survival (OS), that is, β2-microglobulin, anemia, LDH and last therapy (BALL score), was carried out in a substantial number of R/R CLL patients treated either with chemo-immunotherapy or with new drugs, with satisfactory results.[14] In addition, we have proposed a simple and parsimonious prognostic score (survival risk score [SRS]), which seems to perform better than the BALL score and may be universally valuable in predicting OS for BCRi treated patients.[15,16]

The aim of this study was that of comparing the efficacy for OS of IB vs IDELA-R in patients with R/R-CLL in a real-life cohort of 675 patients. All the above-mentioned risk factors were taken into account to have a precise evaluation of the drug efficacy overriding the confounding effects posed by clinical, cellular, or molecular heterogeneity.

2 | MATERIALS AND METHODS

2.1 | Patients

Five hundred and sixty-three cases received IB and 112 cases IDELA-R as salvage therapy outside of clinical trials. Five hundred and forty-one out of 675 derived from a database of an institutional Italian multicenter working group on CLL (Campus CLL). Overall, 21 Italian, one Swiss, and one Israeli center participated this study (see Appendix S1). The final combined database, including R/R CLL patients treated with IB or IDELA-R, was established for research purposes. The database contained clinical information such as age, sex, date of diagnosis, Rai and Binet stage, laboratory parameters, biological markers, treatment history, and date of last follow-up or death, which were obtained from clinical records at the time of inclusion and updated on an ongoing basis. The present analysis was performed in 675 cases, and 630 of them were included in recent papers.[15,16] Patients who had previously received only chemotherapy were included in this study.

2.2 | Immunoglobulin gene mutation and FISH

IGHV mutation analysis and FISH were performed at the reference laboratory of each participating center. The IGHV mutation status was tested on tumor DNA collected at diagnosis and was assessed according to ERIC guidelines.[17] Sequences that differed by more than 2% from their corresponding germ-line sequence were considered mutated.[17-19] FISH analysis was performed on nuclei extracted from fresh or frozen peripheral blood mononuclear cells. The probe used for 17p deletion analysis was LSIp53 (Abbott). At least 200 interphase cells were examined. The presence of 17p deletion abnormality was scored when the percentage of nuclei with the abnormality was above each laboratory's internal cutoff defined as the mean plus 3 standard deviations (SD) of the frequency of normal control cells exhibiting the abnormality.[20]

2.3 | Statistical analysis

Data are expressed as absolute numbers and percentages and between-group comparisons were performed by chi-square test. The effect of study arms on survival was preliminary investigated by Kaplan-Meier analysis, and curves were compared by log rank test. On univariate Cox regression analyses tested covariates for all-cause mortality included allocation arm (IB vs IDELA-R) as well as age, gender, Binet stage, line(s) of therapy, exposure to new drug, time from last therapy, anemia, β2M and LDH serum levels, IGHV mutational status, and TP53 dysfunction evaluated as del(17p). All univariate correlates of mortality as well as all variables, which significantly differed between the two study arms ($P < .1$), were jointly introduced into the same multiple Cox regression model. The potential effect modification by each variable on the allocation arm-mortality link was investigated by assessing the effect of IB vs IDELA-R by the standard linear combination method. In Cox models, data were expressed as hazard ratio, 95% CI, and *P* value. All analyses were performed by SPSS for Windows Version 22, and STATA 13 for Windows StataCorp Lakeway Drive.

3 | RESULTS

Demographic and baseline characteristics as well as prognostic markers are summarized in Table 1. In the IDELA-R group, there was a significantly higher proportion of cases with high-risk features, including older age, lines of previous therapy, abnormal β2-microglobulin, or lactate dehydrogenase (LDH) serum levels, while a trend toward a higher rate of cases with time from last therapy ≤24 months was present in the IB group. Consistently, the intermediate- and high-risk categories of the BALL score (14) (accounting for β2-microglobulin, hemoglobin, LDH values and time from initiation of last therapy) were significantly over-represented in the IDELA-R group, while cases with del(17p) were equally distributed between the two groups (Table 1).

TABLE 1 Comparison of the main clinical and biological features of cases treated with Ibrutinib (I, n = 563) and with Idelalisib-rituximab (IDELA-R, n = 112)

	IB cohort n (%)	IDELA-R cohort n (%)	P*
Age, y			
<65	175 (31.1)	21 (18.8)	**.009**
≥65	388 (68.9)	91 (81.3)	
Sex			
Female	205 (36.4)	37 (33.0)	.52
Male	358 (63.6)	75 (67.0)	
Binet stage			
A	65 (11.5)	7 (6.2)	**.062**
B	248 (44.0)	43 (38.4)	
C	250 (44.5)	62 (55.4)	
Line of therapy[a]			
2nd	228 (40.5)	26 (23.2)	**.001**
>2nd	335 (59.5)	86 (76.8)	
Time from last therapy			
<24 mo	227 (40.3)	34 (30.4)	**.056**
≥24 mo	336 (59.7)	78 (69.6)	
Anemia[b]			
No	330 (58.6)	60 (53.6)	.34
Yes	233 (41.4)	52 (46.4)	
β2-microglobulin			
<5 mg/dL	418 (74.2)	50 (44.6)	**<.0001**
≥5 mg/dL	145 (25.8)	62 (55.4)	
LDH			
Normal	405 (71.9)	69 (61.6)	**.032**
Abnormal	158 (28.1)	43 (38.4)	
BALL Score[c]			
Low risk	371 (65.9)	30 (26.8)	**<.0001**
Intermediate risk	149 (26.5)	64 (57.1)	
High risk	43 (7.6)	18 (16.1)	
IGHV mutational status (n = 667)			
Mutated	179 (32)	46 (42.6)	**.035**
Unmutated	380 (68)	62 (57.4)	
del(17p)			
No	403 (71.6)	86 (76.8)	.29
Yes	160 (28.4)	26 (23.2)	

[a]Median number of lines of therapy is 2 (range 1-9) for IB cohort and 3 (range 1-9) for IDELA-R cohort.

[b]Anemia is Hb <12 g/dL (men) or <11 g/dL (women).

[c]The risk categories of the BALL score are computed as reported in ref. 14.

*Significant *P* values (<.05) are highlighted in bold.

One hundred and nineteen patients (21.1%) discontinued the treatment for toxicity, 67 (11.9%) for CLL progression, and 26 (4.6%) for Richter transformation in the IB group, while 50 patients (44.6%)

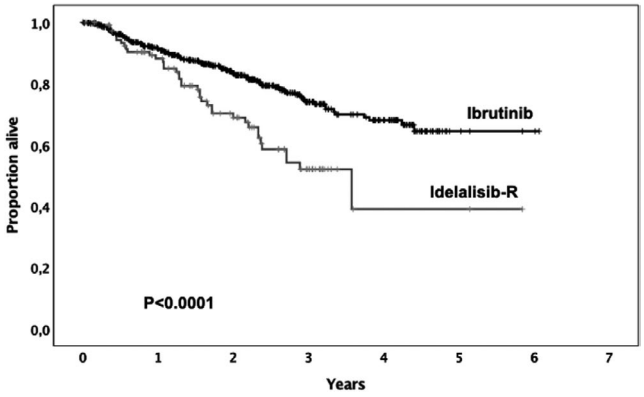

FIGURE 1 Overall survival according to therapy arm

TABLE 2 Univariate Cox regression analyses of all-cause mortality. 0.5, 95% CI 0.34-0.72

Variables	Hazard ratio (95% CI)	P*
Therapy		
Idela-R	1	**<.0001**
Ibrutinib	0.5 (0.34-0.72)	
Age, y		
<65	1	.072
≥65	1.42 (0.97-2.1)	
Binet stage		
A + B	1	**<.0001**
C	1.64 (1.25-2.16)	
Line of therapy		
2nd	1	**<.0001**
>2nd	2.33 (1.53-3.55)	
Time from last therapy		
≥24 mo	1	.06
<24 mo	1.41 (0.98-2.02)	
Anemia[a]		
No	1	**<.0001**
Yes	3.47 (2.44-4.93)	
β2-microglobulin		
<5 mg/dL	1	**<.0001**
≥5 mg/dL	2.33 (1.67-3.24)	
LDH		
Normal	1	**<.0001**
Elevated	2.76 (1.99-3.83)	
IGHV mutational status		
Mutated	1	.65
Unmutated	1.1 (0.76-1.56)	
del(17p)		
No	1	**.001**
Yes	1.72 (1.23-2.41)	

[a]Anemia is Hb <12 g/dL (men) or <11 g/dL (women).

*Significant *P* values (<.05) are highlighted in bold.

TABLE 3 Multivariate Cox regression analyses of all-cause mortality

Variables	Hazard ratio (95% CI)	P*
Therapy		
Idela-R	1	**.032**
Ibrutinib	0.65 (0.44-0.96)	
Age, y		
<65	1	.16
≥65	1.33 (0.89-1.99)	
Binet stage		
A + B	1	.92
C	1.01 (0.76-1.35)	
Line of therapy		
2nd	1	**.005**
>2nd	1.85 (1.20-2.85)	
Time from last therapy		
≥24 mo	1	.37
<24 mo	1.20 (0.80-1.78)	
Anemia[a]		
No	1	**<.001**
Yes	2.70 (1.81-4.02)	
β2-microglobulin		
<5 mg/dL	1	.42
≥5 mg/dL	1.18 (0.79-1.76)	
LDH		
Normal	1	**<.001**
Elevated	1.93 (1.34-2.78)	
IGHV mutational status		
Mutated	1	.37
Unmutated	0.84 (0.582-1.23)	
del(17p)		
No	1	**.003**
Yes	1.70 (1.21-2.40)	

[a]Anemia is Hb <12 g/dL (men) or <11 g/dL (women).
*Significant *P* values (<.05) are highlighted in bold.

discontinued the treatment for toxicity, 16 (14.3%) for CLL progression, and 2 (1.8%) for Richter transformation in the IDELA-R group. The most common toxicities leading to treatment discontinuation were infection (42 cases) and atrial fibrillation (30 cases) for IB cohort and diarrhea (21 cases), infection (15 cases) for IDELA-R cohort. Median duration of treatment was 18 months (range 1-71 months) for IB cohort and 12 months (range 1-54) for IDELA cohort. After a median follow-up of 1.8 years since BCRi start, 143 patients had died (105 [18.7%] and 38 [33.9%] in the IB and in the IDELA-R group, respectively).

An unadjusted analysis of OS (Figure 1) showed that the IB group experienced significantly longer OS than the IDELA-R group (HR IDELA-R vs IB 0.5, 95% CI 0.34-0.72, Table 2).

We adjusted the relationship between allocation groups (IB vs IDELA-R) and mortality for all variables significantly associated with OS at Cox univariate analysis (Table 2), that is, all the four parameters enclosed in the BALL score (14) together with Binet stage C, the number of previous therapies, and del(17p), independently of their different distribution between the two study groups at the study start (Table 1). Furthermore, to increase the efficiency of data adjustment, all variables, associated with outcome at univariate Cox regression analysis (Table 2), were introduced into the multivariate Cox model (Table 3), independently of being different in the two treatment groups at study inception (Table 1). Despite the potential confounders, the protective effect of IB vs IDELA-R (HR = 0.65, 95% CI 0.44-0.96, $P = .032$) was confirmed following the introduction of all these variables as covariates into the multiple Cox regression model (Table 3). Among the other variables, only the number of previous therapies, anemia, high LDH levels, and del(17p) remained independent predictors of OS.

4 | DISCUSSION

Because of the absence of randomized studies, directly confronting IB and IDELA-R, it was decided to investigate a real-life cohort of CLL patients in order to compare the relative efficacy of the two treatments. Although useful in the absence of ad hoc randomized studies, investigations of this type are made complicated by several confounders and particular care should be taken to minimize the so-called "confounding by indication effect." In real-life studies, the potential distortion of the comparison by the two arms (ie, IB and IDELA-R), operated by potential confounders, can be minimized by adjusting for specific and well-known risk factors of OS. Beyond the strategy adopted here, other methods can be selected with the aim of neutralizing the effects of confounders, including the use of instrumental variables (eg, center policy related to the prescription of a given drug) or the propensity score matching. However, the application of these approaches was hampered by the lack of an adequate sample size in our setting, especially in the IDELA-R group.

After the potential confounding factors were neutralized by the selected adjustments, IB proved superior to IDELA-R. A role on the greater IB efficacy in terms of OS length could also be linked to the lower incidence of drug withdrawal due to toxicity. Nevertheless, our finding is in line with previous observations reported by a network metanalysis comparing IB vs IDELA-R in R/R CLL patients.[21] In this metanalysis, the hazard ratio of IB vs IDELA-R was 0.25 (95% CI: 0.12-0.54), a figure lower than that found in our real-life series, suggesting that the context (real-life vs clinical trials) may play a crucial role in determining the magnitude of the effect of IB vs IDELA-R. Furthermore, after stratifying outcomes by first BCRi choice, it has been shown that a large retrospective series of real-life cases, receiving IB as first choice, experienced a significantly longer PFS in the R/R setting.[11] In addition, preliminary results indicate a longer PFS for acalabrutinib, a more selective BTK inhibitor than IB, vs IDELA-R in the ASCEND phase III trial.[22] Finally, our analysis showed

as the number of previous therapies, the anemia, high LDH levels, and del(17p) remained independent prognostic factors in line with previous reports,[1,14] whereas IGHV mutational status did not. These differences are possibly related to the fact that, while IGHV mutational status is just a predictor of potential future progression, anemia and LDH also are indicators of current disease status, that is, of ongoing disease progression and are thus likely altered in patients at later disease stages. This explanation is consistent with the fact that a number of IGHV-mutated patients also can undergo disease progression. The different weight in predicting outcome of IGHV unmutated status and del (17p) in the cohort is consistent with the more powerful predictive characteristics of the latter marker. In conclusion, the analyses of our and of a few other real-life series[11] support the idea that IB could provide some survival advantage compared to another BCRi like IDELA, in association with rituximab, in the R/R-CLL setting. Regrettably, our analysis presents some constraints. Firstly, some concern on the potential for coding errors inherent to any retrospective analysis of claims databases. Furthermore, even though the analyses are adjusted for some characteristics, unmeasured confounding factors may still be present, thereby reducing the statistical power of sub-analyses. Nevertheless, in line with our results, the updated version of ESMO guidelines does not any longer recommend IB and IDELA-R as equal options, but suggest the use IDELA-R merely in patients who are not eligible for any other therapies.[8]

However, the therapeutic algorithms are continuously evolving due to the identification/validation of additional prognostic/predictive factors which may drive the therapeutic choice toward different drugs and/or drug combinations perhaps in specific patients,[23] as well as to the advent of novel effective drugs showing either improved toxicity profiles and/or efficacy/effectiveness both in first and subsequent lines of therapy.[6]

Ultimately, considering the chronic nature of CLL, all the available therapeutic options could be of help over time in the management of the disease.

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CONFLICT OF INTEREST

Nothing to disclose.

AUTHOR CONTRIBUTIONS

FM, MG, MF, GDP, FRM, DR, FDR, A.Cu., GG, LT,AP, AC, RF, and VG designed the study, analyzed and interpreted data, and wrote the manuscript; MG, GT, GD, and FM performed statistical analysis; SB, GC, GF, PM, P.Me., FMR, AZ, IDG, RB, AN, and MF performed central laboratory tests; GR, PS, LL, MC, YH, MV, RM, A.Ch., A.Co., R.Mo., AV, DP, GL, UC, IS, EV, EAM, FM, RC, AR, IA, AB, SG, OJ, and HA provided the patients and collected clinical data; and all authors gave final approval for the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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