SAFETY PROFILE IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA UNDERGOING TREATMENT WITH 1ST AND 2ND GENERATION BRUTON TYROSINE KINASE INHIBITORS: MULTICENTRIC REAL-WORLD EXPERIENCE

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BACKGROUND

- Chronic lymphocytic leukemia (CLL) is the **most frequent leukemia**, being more frequent in older adults.
- Bruton's tyrosine kinase inhibitors **(BTKi) have revolutionized the treatment** displacing immunochemotherapy treatment, along with other targeted therapies, in almost all patient profiles
- **Selectivity of kinome inhibition of these drugs means that the toxicity of first and second generation BTKi are different**, resulting in higher rates of atrial fibrillation and arterial hypertension, mainly in patients treated in the second line or later, while maintaining their efficacy.
- **Real-life studies are needed** to be able to demonstrate these effects in frontline in a more heterogeneous population, without the restrictive exclusion and inclusion criteria required in clinical trials

OBJETIVES

1. Study **the baseline characteristics** of the treated population.
2. Define the **response rate**, and **adverse effect** profile of patients treated with **Ibrutinib or Acalabrutinib** and compare them with each other.

PATIENTS AND METHODS

An observational, retrospective, multicenter, retrospective study was performed. Patients with in **treatment with Ibrutinib or Acalabrutinib in first line or later were included.** Demographic data, comorbidity, cytogenetic and mutational disease data, adverse effect profile, comprehensive geriatric assessment (if applicable) and treatment response evaluation data are collected.

A total of **91 patients** in 4 Spanish centers were included with a median age of 73.22 years (SD 11.06). Fifty-three (58.2%) were male. Fifty-three (58.2%) were treated in frontline, 31.9% (29) in second line and 9.9% (9) in subsequent lines. Acalabrutinib was used in 25 (27.5%) patients and Ibrutinib in 66 (72.5%).
Differences were shown between these two BTKis in terms of line of treatment, with the majority being treated first (P=0.006) and Rai stage, with Rai II predominating (P=0.014). No differences were found between the two BTKis according to the rest of the characteristics.

RESULTS

Table 1. Patients characteristics

	Acalabrutinib N (%) N=25	Ibrutinib N (%) N=66	P
Sex (Male)	16 (64.0%)	44 (66.7%)	1.000
ECOG >2	1 (4.0%)	1 (1.5%)	0.476
RAI Stage			**0.043**
0	0 (0.0%)	5 (7.6%)	
1	9 (36.0%)	13 (19.7%)	
2	9 (36.0%)	21 (31.8%)	
3	6 (24.0%)	9 (13.6%)	
4	1 (4.0%)	18 (27.3%)	
BINET Stage			0.937
A	7 (28.0%)	21 (31.8%)	
B	11 (44.0%)	27 (40.9%)	
C	7 (28.0%)	18 (27.3%)	
CGA			0.475
1	3 (12.0%)	12 (18.2%)	
2	4 (16.0%)	4 (6.1%)	
3	2 (8.0%)	6 (9.1%)	
Comorbidity index >6	13 (52.0%)	36 (54.5%)	1.000
Treatment			**0.013**
Frontline	21 (84.0%)	32 (48.5%)	
2nd	4 (16.0%)	25 (37.9%)	
3nd	0 (0%)	7 (10.6%)	
4nd	0 (0%)	2 (3.0%)	
Anticoagulant use	8 (32.0%)	15 (22.7%)	0.523
Antiagregant use	1 (4.0%)	7 (10.6%)	0.563
Antiarrhymic use	7 (28.0%)	12 (18.2%)	0.459
Antihypertensive use	10 (40.0%)	30 (45.5%)	0.817
Unmutated IgHV	23 (92.0%)	58 (87.9%)	0.853
Mut TP53	6 (24.0%)	14 (21.2%)	0.998
del17p	3 (12.0%)	9 (13.6%)	1.000
del11q	4 (16.0%)	10 (15.2%)	1.000
tri12	5 (20.0%)	16 (24.2%)	0.881
del13q	15 (60.0%)	26 (39.4%)	0.127
Other alterations	1 (4.0%)	5 (7.6%)	0.888
Hypetension	12 (48.0%)	35 (53.0%)	0.846
Diabetes	7 (28.0%)	16 (24.2%)	0.922
Dyslipemia	5 (20.0%)	25 (37.9%)	0.171
Obesity	5 (20.0%)	6 (9.1%)	0.287
Smoking	7 (28.0%)	11 (16.7%)	0.359

Differences were revealed between these two BTKis in terms of line of treatment, with the majority being treated first (P=0.006) and Rai stage, with Rai II predominating (P=0.014). No differences were found between the two BTKis according to the rest of the characteristics.

In terms of toxicity, 14 (15.4%) of patients treated with Ibrutinib developed arterial hypertension, compared to no patients in the Acalabrutinib arm (p=0.009).

With respect to the development of cardiac toxicity, 19 (20.9%) patients suffered some cardiotoxic event, 3 (3.3%) in patients on acalabrutinb and 16 (17.6%) on ibrutinib, with no significant differences found between the two drugs (p=0.2). No significant differences were found with respect to other toxicities (hematologic, digestive, bleeding and infections). Table 2

Table 2. Toxicity profile

Hypertension	**0 (0.0%)**	**14 (21.2%)**	**0.029**
Infection	6 (24.0%)	19 (28.8%)	0.846
Cardiac toxicity	3 (12.0%)	16 (24.2%)	0.320
Bleeding	5 (20.0%)	20 (30.3%)	0.472
Hematological	11 (44.0%)	30 (45.5%)	1.000
Gastrointestinal toxicity	4 (16.0%)	18 (27.3%)	0.397
Other toxicity	6 (24.0%)	17 (25.8%)	1.000
Global toxicity	20 (80.0%)	58 (87.9%)	0.533

No differences in terms of progression-free survival or overall survival were found

Figure 1. Progression free survival

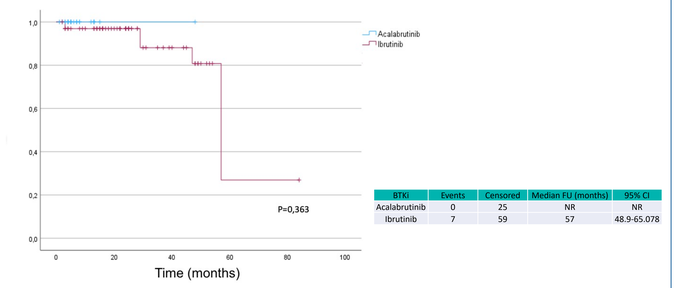
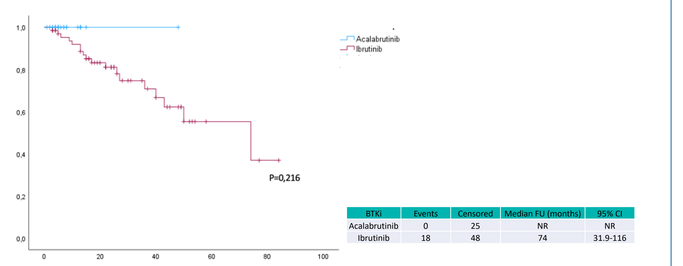


Figure 2. Overall Survival



CONCLUSIONS

BTKI have changed the treatment of CLL, although the second-generation iBTKs have a safer cardiovascular profile and are just as effective in our cohort, even in the frontline.

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