Adverse Effects Of Bruton Tyrosine Kinase Inhibitors In Real World Clinical Practice: The Experience Of A Secondary-Care Hospital.

Ane Brieva López[1], David García Martínez[1], María Ordóñez García[1], Mariana Cerrato Salas[1], Pavel Manuel Acevedo Pérez[1], Juan Sastre Ortega[1] , Juan Carlos Tenécora Quito[1], Esther Jaro Arias[1], Alicia Lorenzo Jambrina[1], Jorge Sánchez- Calero Guillarte[1], M Ángeles Andreu Costa[1].

1. Hospital Universitario de Móstoles. Madrid, Spain.

INTRODUCTION

Bruton tyrosine kinase inhibitors (BTKis) have improved outcomes in B-cell malignancies, particularly chronic lymphocytic leukemia (CLL), compared with chemoimmunotherapy. However, they have a distinct toxicity profile, including cardiovascular adverse events (AEs), especially with ibrutinib.

Methods: We conducted a single-center retrospective observational study of 44 patients with CLL, mantle cell lymphoma, Waldenström macroglobulinemia, marginal zone lymphoma, or other B-cell lymphomas treated with a BTKi, alone or in combination, for ≥3 months at Hospital Universitario de Móstoles. Cardiovascular toxicity included atrial fibrillation, hypertension, and acute coronary syndrome. Results are reported as absolute and relative frequencies.

Purpose: To describe the frequency of AEs associated with ibrutinib, acalabrutinib, and zanubrutinib in patients with B-cell malignancies and their impact on treatment continuation.

RESULTS

Thirty patients (68%) received ibrutinib, six (13%) acalabrutinib, and eight (18%) zanubrutinib. Overall, 80% experienced at least one AE: 86% with ibrutinib, 80% with zanubrutinib, and 50% with acalabrutinib. 61% developed 1–2 AEs and 38% developed >2. Median time to first AE was 4 months (IQR, 2–8). With ibrutinib, cardiovascular toxicity was most frequent (50%), followed by infections (26%). No cardiovascular events occurred with acalabrutinib or zanubrutinib. Bleeding occurred in 9% of ibrutinib-treated and 5% of zanubrutinib-treated patients. In the overall cohort, absolute risks were 35% for cardiovascular toxicity, 40% for infection, and 14% for bleeding. 66% of AEs occurred within the first year, although late events were observed. AEs led to temporary interruption in 52%, permanent discontinuation in 11.7%, dose reduction in 5.8%, and one death.

Table 1. Clinical characteristics, comorbidities, and safety of BTKi therapy at Hospital Universitario de Móstoles.

Sex, n (%)	Male		28 (66,6%)
	Female		14 (33,3%)
Age at diagnosis (median)			42
Pre-existing comorbidities, n (%)	No pre-existing comorbidities		16 (38%)
	Hypertension		21 (50%)
	Atrial fibrillation		1 (2,3%)
	Heart failure		5 (11,9%)
	Chronic kidney disease		3 (7,14%)
	Diabetes mellitus		8 (19%)
	Charlson Comorbidity Index (median)		3
BTKi, n (%)	Ibrutinib		25 (59,5%)
	Ibrutinib combination therapy (with venetoclax/rituximab)		5 (11,9%)
	Acalabrutinib		6 (14,2%)
	Zanubrutinib		8 (19%)
Adverse event during treatment, n (%)	No		8 (20%)
	Yes		34 (80%)
	Cardiovascular toxicity	Atrial fibrillation	7 (16,6%)
		Hypertension	1 (2,3%)
		Acute coronary syndrome	7 (16,6%)
	Arthralgia		2 (4,7%)
	Neutropenia		6 (14,2%)
	Thrombocytopenia		5 (11,9%)
	Hepatotoxicity		3 (7,14%)
	Renal toxicity		5 (11,9%)
	Bleeding		6 (14,2%)
	Cutaneous toxicity		4 (9,5%)
	Infections		17 (40,4%)
Cardiovascular toxicity, n (%)	Ibrutinib		15 (35,7%)
	Acalabrutinib		0
	Zanubrutinib		0
Median time to first AE (months)			4 (2 - 8)
Clinical consequences of AEs, n (%)	No changes		9 (26,4%)
	Dose reduction		2 (5,8%)
	Temporary interruption		18 (52,9%)
	Permanent discontinuation		4 (11,7%)
	Death		1 (2,9%)
Hematologic diagnosis	Ibrutinib		CLL n=18
			MCL n=3
			WM n=3
			MZL n=1
	Acalabrutinib		CLL n=6
	Zanubrutinib		CLL n=6
			WM n=1
	Ibrutinib - Venetoclax		CLL n=5

Table 2. Frequency of adverse events by BTK inhibitor.

AE	Ibrutinib n= 30	Acalabrutinib n= 6	Zanubrutinib n= 8
CV toxicity - atrial fibrillation	7 (23,3%)	0	0
CV toxicity - hypertension	1 (3,33%)	0	0
CV toxicity - acute coronary syndrome	7 (23,3%)	0	0
Bleeding	4 (13,3%)	0	2 (25%)
Infections	11 (36,6%)	1 (16,6%)	5 (25%)
Arthralgia	2 (6,6%)	0	0
Neutropenia	5 (16,6%)	0	1 (12%)
Thrombocytopenia	4 (13,3%)	0	1 (12%)
Hepatotoxicity	1 (3,33%)	2 (33,3%)	0
Cutaneous toxicity	4 (13,3%)	0	0
Renal toxicity	3 (10%)	1 (16%)	1 (12%)

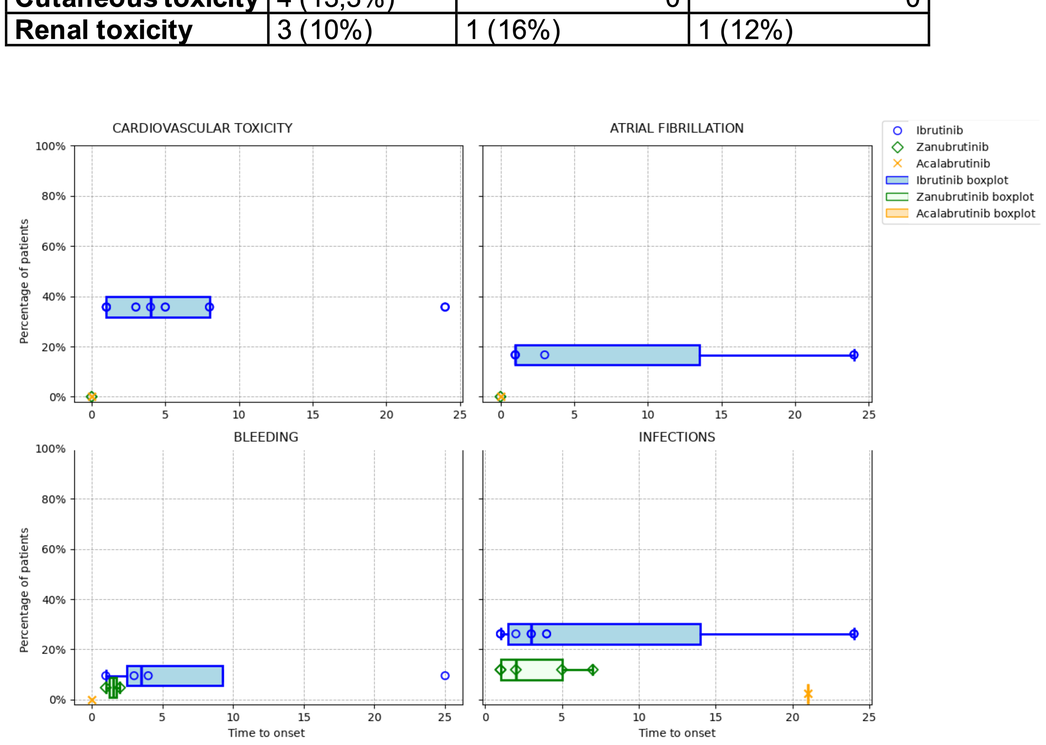

Figure 1. Incidence of cardiovascular toxicity, atrial fibrillation, bleeding, and infections by BTK inhibitors.

CONCLUSION

Ibrutinib was associated with more cardiovascular, infectious, and bleeding events than second-generation BTKis. Comparisons are limited by the small acalabrutinib and zanubrutinib subgroups. Both early and late AEs support continuous monitoring and multidisciplinary management to preserve treatment continuity.

REFERENCES

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CONTACT

Ane Brieva López. brievalopezane@gmail.com