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Real-World Comparative Effectiveness and Safety of BTK Inhibitors Versus Chemoimmunotherapy for Frontline Waldenstrom Macroglobulinemia

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Abstract

Background

No randomized trial has compared Bruton tyrosine kinase inhibitor (BTKi)-based therapy with chemoimmunotherapy (CIT) in frontline Waldenström macroglobulinemia (WM); the RAINBOW trial (NCT04061512) is ongoing. Real-world data are therefore the only current evidence, particularly for older adults, who make up most patients and are underrepresented in trials.

Methods

We conducted a retrospective TriNetX study of adults with WM initiating approved first-line BTKi (ibrutinib or zanubrutinib) or CIT (bendamustine-rituximab or dexamethasone-rituximab-cyclophosphamide). Propensity-score matching used eight prespecified covariates spanning age, sex, race, and hematologic, cardiovascular, and renal comorbidities. The primary outcome was three-year overall survival (OS), and a subgroup analysis of patients aged ≥ 75. One-year safety outcomes are shown in Table 1.

Results

After matching (555/arm), three-year OS was 82.3% with BTKi versus 84.6% with CIT (hazard ratio [HR], 1.08; 95% CI, 0.78-1.50; log-rank P=.637). Among patients ≥75 years (167/arm), OS was 79.2% versus 76.0% (HR, 0.83; 95% CI, 0.49-1.41; P=.49), favoring BTKi but not statistically significant. BTKi was associated with significantly lower (all P<.05) serious infection (3.6% vs 7.0%; RR, 0.52), cytopenias (13.5% vs 31.2%; RR, 0.43), hospitalization (25.4% vs 40.4%; RR, 0.63), and transfusion (4.3% vs 12.5%; RR, 0.35; n=554/arm), and significantly more atrial fibrillation/flutter (8.1% vs 3.6%; RR, 2.23; P=.003). Pretreatment hemoglobin was lower among CIT initiators than BTKi initiators (10.4 vs 11.1 g/dL).

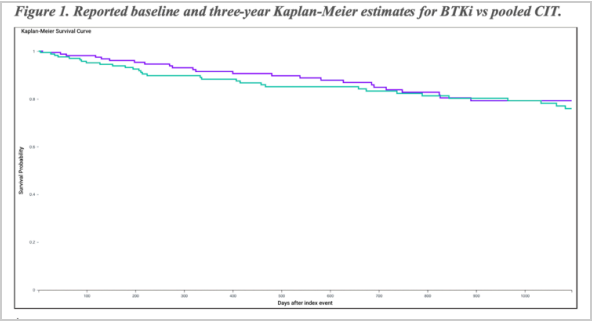


Figure 1. Reported baseline and three-year Kaplan-Meier estimates for BTKi vs pooled CIT.

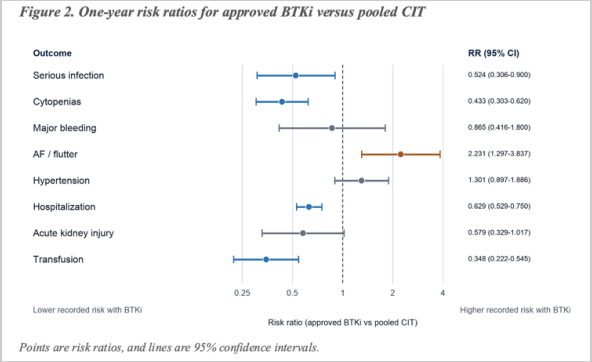


Figure 2. One-year risk ratios for approved BTKi versus pooled CIT

Table 1. Three-year survival and one-year clinical outcomes of propensity-matched cohorts

Outcome	BTKi	Pooled CIT	Relative estimate (95% CI)	P value
Three-year KM survival	82.29%	84.62%	HR 1.081 (0.781-1.496)	0.6372
Serious infection	3.65%	6.96%	RR 0.524 (0.306-0.900)	0.0168
Cytopenias	13.49%	31.16%	RR 0.433 (0.303-0.620)	<0.0001
Major bleeding	2.47%	2.86%	RR 0.865 (0.416-1.800)	0.6979
Atrial fibrillation/flutter	8.10%	3.63%	RR 2.231 (1.297-3.837)	0.0028
Hypertension	16.17%	12.43%	RR 1.301 (0.897-1.886)	0.1633
Hospitalization	25.41%	40.36%	RR 0.629 (0.529-0.750)	<0.0001
Acute kidney injury	3.67%	6.34%	RR 0.579 (0.329-1.017)	0.0536
Transfusion	24/554* (4.33%)	69/554* (12.46%)	RR 0.348 (0.222-0.545)	<0.0001

**Transfusion denominator is 554/arm (vs 555 matched) owing to 1 patient per arm with missing transfusion data.*

Table 1. Three-year survival and one-year clinical outcomes of propensity-matched cohorts

Conclusion

BTKi and CIT produced similar three-year OS overall and among patients ≥75 years, a novel comparison given the absence of randomized data. BTKi was associated with significantly fewer infections, cytopenias, hospitalizations, and transfusions, while the higher rate of atrial fibrillation/flutter with BTKi and cytopenias with CIT reflect established toxicities of each regimen. Higher baseline hemoglobin among BTKi initiators may partly explain the hematologic-toxicity gap. Both arms pooled agents with differing toxicity profiles (ibrutinib/zanubrutinib; bendamustine-rituximab/DRC); agent-level data are needed to confirm these findings prospectively.

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