CLL Obesity Heightens Infection Risk in CLL Patients Treated with BTK inhibitors

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Introduction

Patients with chronic lymphocytic leukemia (CLL) are at elevated risk for infections due to impaired immune function, with hypogammaglobulinemia being a major contributor. Treatment with Bruton tyrosine kinase inhibitors (BTKi), particularly ibrutinib, further increases infection susceptibility. Obesity, a condition marked by chronic low-grade inflammation, may also impact immune responses. While some studies suggest obesity can confer survival benefits in various diseases, its effect on infection risk in BTKi-treated CLL patients is unclear. This study aimed to evaluate the 5-year infection risk in obese CLL patients receiving BTKi therapy using a large real-world dataset.

Methods

We utilized the TriNetX Global Collaborative Network to identify patients receiving Ibrutinib, acalabrutinib, or Zanubrutinib as a first line of treatment for CLL. Patients with prior chemoimmunotherapy or venetoclax use were excluded. The propensity score matched was adjusted for age and sex. Cohorts were established using the body mass index. Risk ratios (RRs), 95% confidence intervals (CI), and p-values were calculated. Log-rank test was used for survival analysis.

FIGURE 1.

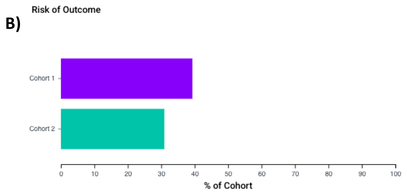
A)

Cohort Statistics

	Cohort	Patients in Cohort	Patients with Outcome	Risk
1	Obesity Class III BTK	608	239	39.309%
2	Normal BMI BTK	608	188	30.921%

Risk Difference				Risk Ratio		Odds Ratio	
Risk Difference	95 % CI	z	p	Risk Ratio	95 % CI	Odds Ratio	95 % CI
8.388%	(3.043%,13.733%)	3.064	0.0022	1.271	(1.089,1.484)	1.447	(1.142,1.834)

B)



C)

Cohort Statistics

	Cohort	Patients in Cohort	Patients with Outcome	Median Survival (Days)	Survival Probability at End of Time Window	Log-Rank Test χ^2	df	p
1	Obesity Class III BTK	608	239	1,211	38.986%	18.086	1	< 0.0001
2	Normal BMI BTK	608	188	-	51.316%			

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Hazard Ratio		Proportionality		
Hazard Ratio	95 % CI	χ^2	df	p
1.511	(1.248,1.83)	1.02	1	0.3124

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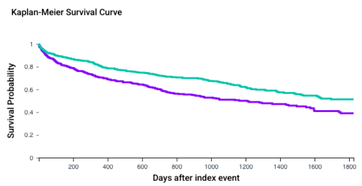


FIGURE 1. In CLL patients treated with BTK inhibitors, infection incidence was highest among those with class III obesity (39.3%) compared with normal BMI (30.9%; RR 1.27, 95% CI 1.09–1.48; p=0.0022) (Figure 1A-B). These patients also had lower 5-year infection-free survival (38.98% vs. 51.31%, p<0.0001) (Figure 1C-D). Infection risk decreased progressively with lower obesity classes and was not significantly different between overweight and normal-BMI patient (Data not shown).

FIGURE 2.

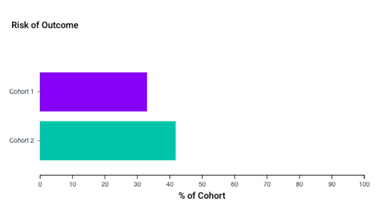
A)

Cohort Statistics

	Cohort	Patients in Cohort	Patients with Outcome	Risk
1	BMI>40 others BTKi	272	90	33.088%
2	BMI>40 Ibrutinib	272	114	41.912%

Risk Difference				Risk Ratio		Odds Ratio	
Risk Difference	95 % CI	z	p	Risk Ratio	95 % CI	Odds Ratio	95 % CI
-8.824%	(-16.926%,-0.721%)	-2.125	0.0335	0.789	(0.634,0.983)	0.685	(0.483,0.972)

B)



C)

Cohort Statistics

	Cohort	Patients in Cohort	Patients with Outcome	Median Survival (Days)	Survival Probability at End of Time Window	Log-Rank Test χ^2	df	p
1	BMI>40 others BTKi	272	90	943	27.962%	0.878	1	0.3487
2	BMI>40 Ibrutinib	272	114	1,280	38.269%			

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Hazard Ratio		Proportionality		
Hazard Ratio	95 % CI	χ^2	df	p
1.146	(0.861,1.524)	2.383	1	0.1227

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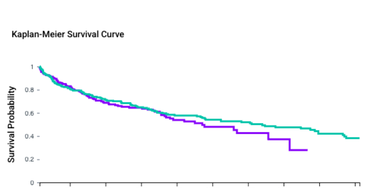


FIGURE 2. In CLL patients with class III obesity, infection risk remained elevated with second-generation BTK inhibitors but was lower compared with ibrutinib (RR 0.79, 95% CI 0.63–0.98; p=0.03) (Figure 2A-B). However, the difference in 5-year infection-free survival was not significant (p=0.34) (Figure 2C-D).

FIGURE 3.

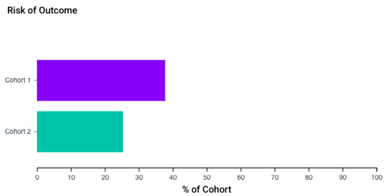
A)

Cohort Statistics

	Cohort	Patients in Cohort	Patients with Outcome	Risk
1	Obesity Class III BTK	588	222	37.755%
2	Untreated CLL BMI>40	588	149	25.34%

Risk Difference				Risk Ratio		Odds Ratio	
Risk Difference	95 % CI	z	p	Risk Ratio	95 % CI	Odds Ratio	95 % CI
12.415%	(7.151%,17.679%)	4.581	< 0.0001	1.49	(1.253,1.772)	1.787	(1.392,2.294)

B)



C)

Cohort Statistics

	Cohort	Patients in Cohort	Patients with Outcome	Median Survival (Days)	Survival Probability at End of Time Window	Log-Rank Test χ^2	df	p
1	Obesity Class III BTK	588	222	1,211	38.178%	16.246	1	< 0.0001
2	Untreated CLL BMI>40	588	149	-	55.421%			

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Hazard Ratio		Proportionality		
Hazard Ratio	95 % CI	χ^2	df	p
1.53	(1.242,1.884)	1.383	1	0.2396

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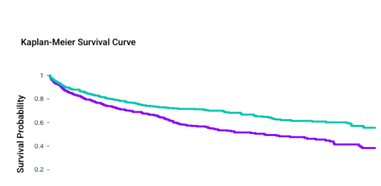


FIGURE 3. In CLL patients with BMI ≥40, those receiving BTK inhibitors had a significantly higher risk of infections compared with untreated CLL patients of similar BMI (RR 1.49, 95% CI 1.25–1.77; p<0.0001) (Figure 3A-B). . These patients also had lower 5-year infection-free survival (38.17% vs. 55.42%, p<0.0001) (Figure 3C-D).

FIGURE 4.

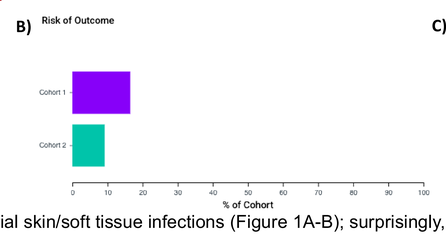
A)

Cohort Statistics

	Cohort	Patients in Cohort	Patients with Outcome	Risk
1	Obesity Class III BTK	608	100	16.447%
2	Normal BMI BTK	608	56	9.211%

Risk Difference				Risk Ratio		Odds Ratio	
Risk Difference	95 % CI	z	p	Risk Ratio	95 % CI	Odds Ratio	95 % CI
7.237%	(3.5%,10.974%)	3.773	0.0002	1.786	(1.313,2.428)	1.94	(1.369,2.75)

B)



C)

Cohort Statistics

	Cohort	Patients in Cohort	Patients with Outcome	Risk
1	Obesity Class III BTK	608	110	18.092%
2	Normal BMI BTK	608	106	17.434%

Risk Difference				Risk Ratio		Odds Ratio	
Risk Difference	95 % CI	z	p	Risk Ratio	95 % CI	Odds Ratio	95 % CI
0.658%	(-3.638%,4.954%)	0.3	0.7641	1.038	(0.815,1.322)	1.046	(0.779,1.404)

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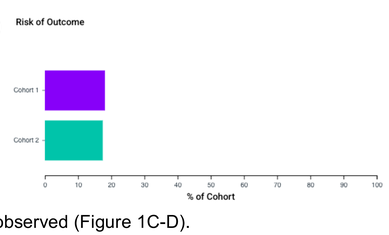


FIGURE 4. Most common infections were bacterial skin/soft tissue infections (Figure 1A-B); surprisingly, no significant difference in pneumonia rates was observed (Figure 1C-D).

Conclusions

- In CLL patients on BTK inhibitors, class III obesity (BMI ≥40) had the highest infection incidence and lower 5-year infection-free survival vs. normal BMI.
- Among class III obese patients, second-generation BTK inhibitors were associated with a reduced infection risk compared with ibrutinib, although 5-year infection-free survival did not differ.
- BTKi-treated CLL patients had higher infection risk and worse infection-free survival than untreated patients of similar BMI.
- The most frequent infections were bacterial skin/soft tissue infections, while pneumonia rates did not differ significantly.