Bruton's Tyrosine Kinase Inhibitors in B-Cell Lymphoma and Risk of Infection: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background

Immunodeficiencies in B-Cell Lymphoma:
B-cell lymphoma patients face increased infection risks due to compromised immunity, characterized by:

- Cell-Mediated Immunity Defects
- Hypogammaglobulinemia: Mainly affects IgG3 and IgG4
- Neutrophil and Monocyte Dysfunction
- Complement Deficiencies (1-2)

Bruton's Tyrosine Kinase (BTK) Inhibitors in Treatment:
Treatment strategies vary by malignancy type, patient age, and disease stage, with BTK inhibitors like ibrutinib, acalabrutinib, zanubrutinib, and pirtobrutinib playing a crucial role.
Approved by the FDA, these drugs enhance progression-free and overall survival but increase severe infection risks, necessitating vigilant monitoring and prophylactic strategies (3-5).

Objective

This study aimed to estimate the incidence and risk of severe (Grade ≥ III) infections among patients with B-cell lymphoma undergoing monotherapy with BTK inhibitors.

Methods

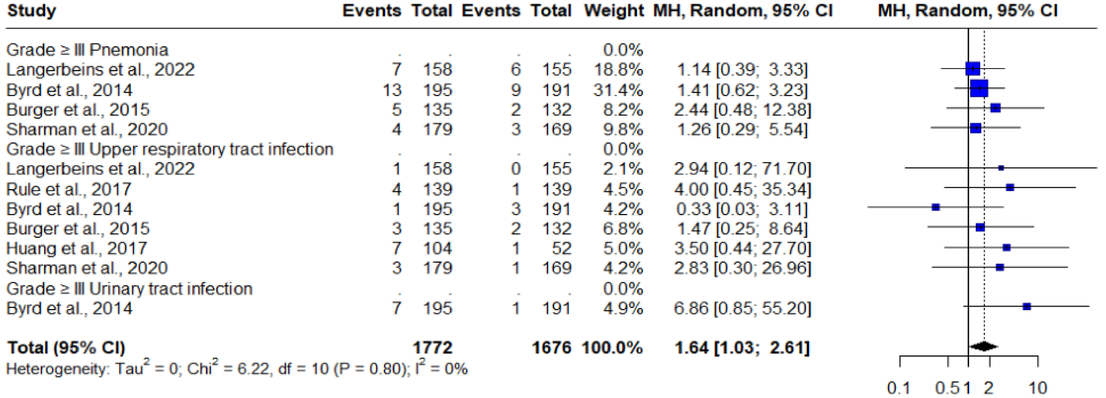
Search Databases: MEDLINE/PubMed, Embase, and Web of Science from their inception to October 4, 2023
Additional Sources: We also reviewed clinicaltrials.gov, relevant bibliographies, and conference abstracts to identify further studies
Inclusion Criteria: We included randomized controlled trials (RCTs) that reported on infections in patients with any type of B-cell lymphoma treated with BTK inhibitor monotherapy.
Variables Extracted: Included study characteristics, treatment specifics, patient demographics, and outcomes concerning Grade ≥III infections
Risk of Bias: Assessed using the Cochrane Risk of Bias tool (ROB 2)
Meta-Analysis Eligibility: RCTs comparing BTKi monotherapy against any systemic therapy as the comparator were synthesized quantitatively.
Analytical Method: Employed a random-effects model to calculate the risk ratio (RR) using the Mantel-Haenszel method.
Software Used: Analysis conducted using R Statistical Software, version 4.3.2

Results

Table 1. Risk of Grade ≥ III Infections in B-Cell Lymphoma Patients: BTK Inhibitors vs. Comparators

Author, year, trial	Treatment arm	N	Grade	Pneumonia	Infections	Upper respiratory tract infection	Urinary tract infection
Langerbeins et al., 2022	Ibrutinib	158	Grade III	7 (4.4%)	-	1 (0.6%)	-
NCT02863718	Placebo	155	Grade III	6 (3.9%)	-	0	-
Rule et al., 2017	Ibrutinib	139	Grade ≥ III	-	-	4 (2.2%)	-
NCT01646021	Temsirolimus	139	Grade ≥ III	-	-	1 (0.7%)	-
Hillman et al., 2022	Zanubrutinib	204	Grade ≥ III	8 (3.9%)	26 (13%)		
NCT03734016	Ibrutinib	207	Grade ≥ III	10 (4.8%)	37 (18%)	-	-
Burger et al., 2015	Ibrutinib	135	Grade III	5 (4%)	-	3 (2%)	-
NCT01722487	Chlorambucil	132	Grade III	2 (2%)	-	2 (2%)	-
Byrd et al., 2021	Acalabrutinib	266	Grade III	28 (11%)	-	5 (1.9%)	3 (1.1%)
NCT02477696	Ibrutinib	263	Grade III	23 (8.7%)	-	1 (0.4%)	6 (2.3%)
Byrd et al., 2014	Ibrutinib	195	Grade III-IV	13 (7%)	-	1 (1%)	7 (4%)
NCT01578707	Ofatumumab	191	Grade III-IV	9 (5%)	-	3 (2%)	1 (1%)
Burger et al., 2019	Ibrutinib	104	Grade III-IV	-	6 (5.8%)	3 (2.9%)	2 (1.9%)
NCT02007044	Ibrutinib + rituximab	104	Grade III-IV	-	3 (2.9%)	1 (1%)	0
Dimopoulos et al., 2023	Ibrutinib	98	Grade ≥ III	10 (10%)	27 (28%)	1 (1%)	-
NCT03053440	Zanubrutinib	101	Grade ≥ III	1 (1%)	22 (22%)	0	-
Sharman et al., 2020	Acalabrutinib	179	Grade ≥ III	4 (2.2%)	-	3 (1.7%)	0
NCT02475681	Acalabrutinib + Obinutuzumab	178	Grade ≥ III	10 (5.6%)	-	4 (2.2%)	1 (0.6%)
	Obinutuzumab + Chlorambucil	169	Grade ≥ III	3 (1.8%)	-	1 (0.6%)	0
Woyach et al., 2018	Ibrutinib	180	Grade III	-	29 (16%)	-	-
NCT01886872			Grade IV	-	6 (3%)	-	-
			Grade V	-	2 (1%)	-	-
	Ibrutinib + rituximab	181	Grade III	-	28 (15%)	-	-
			Grade IV	-	7 (4%)	-	-
			Grade V	-	2 (1%)	-	-
	Bendamustine + rituximab	176	Grade III	-	17 (10%)	-	-
			Grade IV	-	6 (3%)	-	-
			Grade V	-	3 (2%)	-	-
Huang et al., 2017	Ibrutinib	104	Grade ≥ III	-	-	7 (6.7%)	-
NCT01973387	Rituximab	52	Grade ≥ III	-	-	1 (1.9%)	-

Figure 1. Meta-Analysis of the Risk of Severe (Grade ≥ III) Infections in Patients with B-cell Lymphoma Treated with BTK Inhibitor Monotherapy



Study Retrieval and Selection

- Initial search retrieved 3,289 studies from databases
- 11 studies met inclusion criteria; 6 were analyzed in the meta-analysis

Participant Overview

- Median age varied from 64 to 73 years
- Follow-up between 9.4 and 44.4 months

Analysis Group Details

- Intervention Group: Included 1,772 patients on BTK inhibitors (BTKi)
- Comparator Group: Consisted of 1,676 patients receiving other treatments

Key Findings on Infection Risks

- Infection Severity: Higher occurrence of Grade ≥ III infections (such as pneumonia, upper respiratory, and urinary tract infections) in the BTKi group
- Risk Ratio (RR): 1.64 – patients on BTKi had a 64% higher risk of developing severe infections
- Confidence Interval (CI): 95% CI from 1.03 to 2.61, indicating a statistically significant result

Conclusion

Patients with B-cell lymphoma who are treated with BTK inhibitor monotherapy have an increased risk of developing severe infections.

Clinicians prescribing BTK inhibitor monotherapy should be vigilant about the potential for infectious complications.

It is critical to monitor these patients closely for any signs of infection and to implement effective prophylactic strategies to mitigate this risk.

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