Risk of Infection with Ibrutinib in Patients with Chronic Lymphocytic Leukemia: A Systematic Review and Meta-analysis of Phase III Randomized Controlled Trials

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Background

- Ibrutinib is an oral Bruton's tyrosine kinase (BTK) inhibitor which has transformed the management of several B-cell malignancies.
- B-cell malignancies including CLL confer increased risk of infections owing to defects in the innate and adaptive immunity.
- Recent studies have provided conflicting data on the risk of infection with ibrutinib.
- We conducted a systematic review and meta-analysis of all phase III randomized controlled trials (RCT) to determine the relative risk of infection associated with the ibrutinib in patients with CLL.

Methods

Literature search

- We performed a systematic search of Embase, PubMed, Web of Science, Scopus, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Clinical Trials.gov with appropriate keywords through 07/10/18.

Eligibility criteria

- All randomized controlled trials comparing ibrutinib with other agents or placebo in patients with CLL and also reporting infection as a treatment-emergent adverse event.

Data extraction

- The search strategy, study selection, data extraction, and analysis adhered to the PRISMA guidelines.
- After removing duplicates, 2403 records were screened for further eligibility by two independent reviewers.

Data synthesis and analysis

- We pooled the point estimates using random effects model of the generic inverse variance method (Der Simonian and Laird).
- Statistical analyses were performed using the Stata/SE 15.1 (StataCorp LP, College Station, TX, USA).
- Calculated pooled risk ratio (RR) with 95% confidence interval (CI).
- Heterogeneity was assessed using I^2 statistic.

Methods

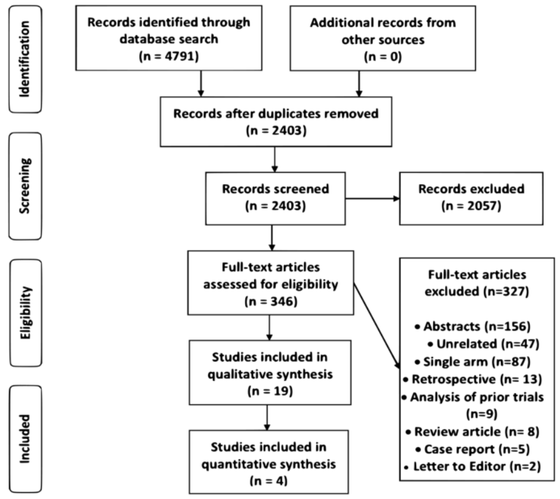
- Publication bias was assessed by using Funnel plot.

Results

Search results

- Finally, 4 RCTs including 1383 patients (721 in ibrutinib arm and 662 in control arm) were included in quantitative synthesis. (Fig 1).

Fig. 1 Flow diagram of the study selection process



Characteristics of the studies

- Median duration of ibrutinib therapy across studies - 17.7 months (range 9.4 - 18.4)
- Ibrutinib used as 1st line therapy in RESONATE-2, in relapsed/ refractory setting in other trials.
- Ibrutinib was compared to placebo in HELIOS, where both groups received concomitant therapy with bendamustine/ rituximab.
- The comparator arm used ofatumumab in RESONATE, chlorambucil in RESONATE-2, and rituximab in study by Huang et al. (Table 1, 2).

Results

Table 1. Characteristics of the studies in meta-analysis

Study Name	Author	Year	Ibrutinib daily dose (mg)	Median duration of Ibrutinib (mo)	Line of therapy	Comparator	Concomitant therapy in both groups	Total no. of patients	
								Ibrutinib	Other
RESONATE	Byrd et al.	2014	420	9.4	>1	Ofatumumab	N/A	195	191
RESONATE-2	Burger et al.	2015	420	18.4	1	Chlorambucil	N/A	135	132
HELIOS	Khan et al.	2016	420	17.0	>1	Placebo	BR	287	287
N/A	Huang et al.	2018	420	16.4	>1	Rituximab	N/A	104	52
								721	**662**

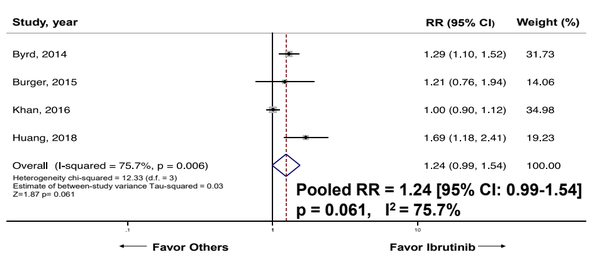
Table 2. Infection rate across studies

Frontline	**Ibrutinib [n (%)]**	**Control [n (%)]**
Total infections	31 (22%)	25 (18%)
Pneumonia	5 (3%)	2 (1%)
URTI	23 (17%)	23 (17%)
Relapsed Refractory	**Ibrutinib [n (%)]**	**Control [n (%)]**
Total infections	409 (69%)	325 (61%)
Pneumonia	55 (11%)	49 (10%)
URTI	100 (17%)	75 (14%)

Meta-analysis

- Pooled RR for total infection (any grade) with ibrutinib vs. control was **1.24 [95% CI 0.99- 1.54, p=0.061**, I^2= 75.7%]. (Fig. 2A)
- Risk of pneumonia (grade 3-5) was not significantly different in ibrutinib arm; **RR 1.19 [95%CI: 0.76-1.88, p=0.448**, I^2=0.0%]. (Fig. 2B)
- Ibrutinib was not associated with a significantly higher risk of URTI (any grade), compared to control group; **RR 1.16 [95%CI: 0.86-1.56, p=0.341**, I^2=25.4%]. (Fig. 2C)

Fig 2A. Pooled RR of total infection (any grade) in patients with CLL - Ibrutinib vs. control



Results

Fig 2B. Pooled RR of Pneumonia (grade 3-5) in patients with CLL- Ibrutinib vs. control

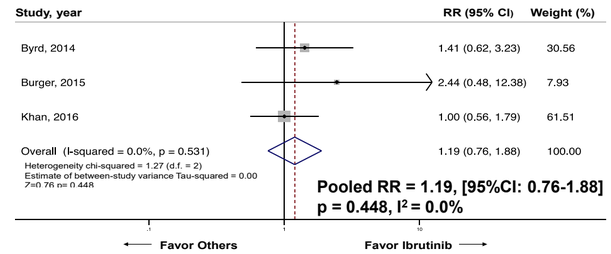
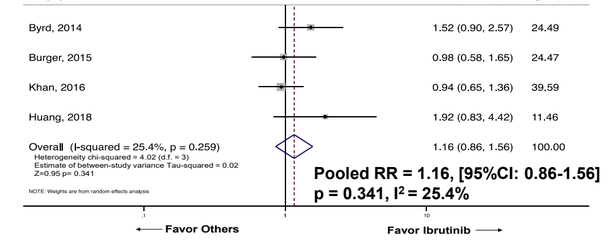


Fig 2C. Pooled RR of URTI (any grade) in patients with CLL- Ibrutinib vs. control



Conclusions

- Our study showed a trend towards significant increase in total infection with ibrutinib, compared to control group in CLL patients.
- Risk of pneumonia and URTI did not differ significantly between study arms.
- Patients on ibrutinib should be vigilantly monitored for infection

Selected References

1. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371:213-223.
2. Sun C, Tian X, Lee YS, et al. Partial reconstitution of humoral immunity and fewer infections in patients with chronic lymphocytic leukemia treated with ibrutinib. Blood. 2015; 126: 2213-9.
3. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med. 2015; 373: 2425-37.

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