Risk of atrial fibrillation and pulmonary toxicities in patients with hematologic malignancies treated with ibrutinib

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INTRODUCTION

Ibrutinib is an oral potent, covalent inhibitor of bruton’s tyrosine kinase (BTK), a kinase downstream of the B-cell receptor which involves in the B cell survival and proliferation.

Ibrutinib has shown to improve survival in many B-cell malignancies with noteworthy safety concerns.

We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to determine the risk of atrial fibrillation and pulmonary toxicities in patients with hematologic malignancies treated with ibrutinib.

METHODS

LITERATURE SEARCH

- We performed a comprehensive literature search using MEDLINE, EMBASE databases and meeting abstracts through July 31, 2018.
- The references of all potential studies were also reviewed for any additional relevant studies.
- All databases and meeting abstracts were systematically searched with the keywords ‘ibrutinib’ OR ‘PCI-32765’ OR ‘bruton’s tyrosine kinase inhibitors’.
- We limited the search to ‘humans’ and ‘controlled clinical trials’.
- All studies written in English or non-English languages were obtained.

ELIGIBILITY CRITERIA

- The studies that were eligible to be included in the meta-analysis had to conform with the following characteristics:
  1. Phase 3 RCTs comparing ibrutinib and a control group; and
  2. Phase 3 RCTs that mentions atrial fibrillation and pulmonary toxicities as adverse effects.

DATA EXTRACTION

- Three authors screened independently for eligibility and conducted data extraction from each eligible study.
- Disagreements were resolved by other two reviewers.

STUDY OUTCOME MEASURES

- The endpoint of our meta-analysis was atrial fibrillation and pulmonary toxicities as adverse effects.

DATA SYNTHESIS AND ANALYSIS

- Mantel-Haenszel (MH) method was utilized to calculate the pooled absolute risk ratio with 95% confidence interval (CI).
- Random effects model was applied.
- P value less than 0.05 were considered significant.

RESULTS

Search results

- A total of 1811 patients with chronic lymphocytic leukemia/ small lymphocytic lymphoma, mantle-cell lymphoma and Waldenstrom’s macroglobulinemia from six phase 3 RCTs were eligible.
- Figure 1 demonstrates the comprehensive steps of study selection.

Characteristics of the studies

- The characteristics of the studies were demonstrated completely in Table 1.
- Studies compared ibrutinib vs ofatumumab, ibrutinib vs chlorambucil, ibrutinib + bendamustine + rituximab vs placebo + bendamustine + rituximab, ibrutinib vs temsirolimus and ibrutinib vs rituximab were included in the analysis.
- The randomization ratio was 1 to 1 in all studies except Huang et al.

Fig. 1 Flow diagram of the study selection process

Table 1 Characteristics of the studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Phase</th>
<th>Treatment</th>
<th>Eligibility</th>
<th>Feasibility</th>
<th>Randomization</th>
<th>Atrial Fibrillation</th>
<th>Pulmonary Toxicity</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>3</td>
<td>Placebo + bendamustine + rituximab</td>
<td>High risk</td>
<td>Yes</td>
<td>1:1</td>
<td>0.0001</td>
<td>0.0001</td>
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<td>3</td>
<td>Placebo + rituximab</td>
<td>Low risk</td>
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<td>1:1</td>
<td>0.028</td>
<td>0.043</td>
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<tr>
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<td>3</td>
<td>Temsirolimus</td>
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<td>1:1</td>
<td>0.001</td>
<td>0.002</td>
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<td>1:1</td>
<td>0.001</td>
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Table 2 Characteristics of the studies included in the meta-analysis

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CONCLUSION

- Our meta-analysis demonstrated that patients on ibrutinib noted a significant increase in the risk of atrial fibrillation with a relative risk of 3.748.
- However, the risk of pulmonary toxicities was not statistically increased in the ibrutinib group.

REFERENCES