INTRODUCTION

- Chronic lymphocytic leukemia is the most common adult leukemia and the B-cell receptor signaling pathway via Bruton's tyrosine kinase is shown to involve in the pathogenesis.
- Ibrutinib, an oral Bruton's tyrosine kinase inhibitor, has become frontier in chronic lymphocytic leukemia or small lymphocytic lymphoma.
- We undertook a systematic review and pooled analysis of randomized controlled trials to determine the risk of hematological toxicities and health-related quality of life events in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma 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 ‘Ibrutinib’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 III RCTs comparing ibrutinib and a control group; and
  2. Phase III RCTs that mention hematological toxicities and health-related quality of life events as adverse effects.

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

study outcome measures
- The endpoint of our meta-analysis was hematological toxicities and health-related quality of life events 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
- Four phase III randomized controlled trials with a total of 1383 patients with chronic lymphocytic leukemia or small lymphocytic lymphoma 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, and ibrutinib vs rituximab were included in the analysis.
- The randomization ratio was 1 to 1 in all studies except Huang et al. (2014).

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

<table>
<thead>
<tr>
<th>Study type</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Comparator</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter randomized controlled trial</td>
<td>Ibrutinib + Bendamustine + Rituximab</td>
<td>3 years</td>
<td>Placebo + Bendamustine + Rituximab</td>
<td>ibrutinib group vs 40 (6.042%) in control arm</td>
</tr>
<tr>
<td>Multicenter randomized controlled trial</td>
<td>Ibrutinib vs Chlorambucil</td>
<td>2 years</td>
<td>Chlorambucil</td>
<td>ibrutinib group vs 40 (6.042%) in control arm</td>
</tr>
<tr>
<td>Multicenter randomized controlled trial</td>
<td>Ibrutinib vs Placebo</td>
<td>2 years</td>
<td>Placebo</td>
<td>ibrutinib group vs 40 (6.042%) in control arm</td>
</tr>
<tr>
<td>Single center randomized controlled trial</td>
<td>Ibrutinib vs Ofatumumab</td>
<td>2 years</td>
<td>Ofatumumab</td>
<td>ibrutinib group vs 40 (6.042%) in control arm</td>
</tr>
</tbody>
</table>

META-ANALYSIS

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>RR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>0.999 (0.798 – 1.305)</td>
<td>0.997</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0.911 (0.798 – 1.037)</td>
<td>0.196</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0.928 (0.798 – 1.074)</td>
<td>0.377</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.850 (0.723 – 1.000)</td>
<td>0.044</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0.798 (0.620 – 1.024)</td>
<td>0.091</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0.746 (0.620 – 0.902)</td>
<td>0.004</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0.651 (0.485 – 0.877)</td>
<td>0.007</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>0.693 (0.558 – 0.861)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

CONCLUSION

- Ibrutinib increased the risk of all-grade thrombocytopenia, arthralgia and muscle spasms whereas the risk of high-grade anemia was significantly lower in ibrutinib arm compared to control group, favoring ibrutinib.

REFERENCES