Ibrutinib Associated Bleeding: Major or Minor?

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Objectives

• Incidence
• Mechanism
• Risk Factors
• Recommendation
Ibrutinib

• Irreversible inhibitor of Bruton’s tyrosine kinase (BTK)
• Approved for Chronic Lymphocytic Leukemia (CLL/SLL), Mantel Cell Lymphoma (MCL), Marginal Zone Lymphoma, Waldenström macroglobulinemia
• Side effects increased risk of bleeding & atrial fibrillation
• Cytochrome P450 3A (CYP3A) metabolism
Incidence of Bleeding in MCL RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease &amp; Follow-Up</th>
<th>Grade 1-2</th>
<th>Grade 3-4</th>
<th>Fatal Bleed</th>
<th>Exclude Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dreyling Lancen 2016</td>
<td>MCL (n=139), 20 mo</td>
<td>N.R.</td>
<td>10% (6%/yr)</td>
<td>0%</td>
<td>Yes</td>
</tr>
<tr>
<td>Wang Blood 2015</td>
<td>MCL (n=111), 27 mo</td>
<td>44%</td>
<td>6% (2.7%/yr)</td>
<td>0%</td>
<td>Later</td>
</tr>
</tbody>
</table>

- Most common type of grade 1-2 bleeding: subcutaneous or mucosal (contusion, epistaxis, petechiae, hematuria, ecchymosis)
- Bleeding events higher in patients with anticoagulation (AC: LMWH 14%, warfarin 10%) or antiplatelet (AP: ASA 26%, clopidogrel 6%)
  - AC/AP: 69% any grade, 8% grade 3-4 => protocol amendment to exclude VKA
  - None: 28% any grade, 4% grade 3-4
Incidences of Bleeding in CLL/SLL RCTs

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Burger NEJM 2015</td>
<td>CLL (n=136), 18 mo</td>
<td>N.R.</td>
<td>4% (2.7%/yr)</td>
<td>0%</td>
<td>Yes</td>
</tr>
<tr>
<td>Byrd NEJM 2014</td>
<td>CLL (n=195), 9 mo</td>
<td>44%</td>
<td>1% (1.3%/yr)</td>
<td>0%</td>
<td>Yes</td>
</tr>
<tr>
<td>Byrd Blood 2015</td>
<td>CLL (n=132), 36 mo</td>
<td>53%</td>
<td>8% (2.7%/yr)</td>
<td>0.7%</td>
<td>Later</td>
</tr>
</tbody>
</table>

- 20% patients received concurrent anticoagulants:
  - LMWH 15%, VKA 3%, UFH 2%, dabigatran 1%, rivaroxaban <1%, apixaban <1%
- 43% patients received concurrent antiplatelets:
  - NSAIDs 28%, ASA 21%, clopidogrel 2%
- No data on comparison with concurrent AC/AP vs. without in CLL

Jones, ASH 2014 annual meeting presentation
Incidence of Bleeding in Cohort Studies

• RCTs of ibrutinib:
  • Excluded concurrent medications by CYP3A
  • Excluded concurrent warfarin use (did not restrict other anticoagulant)

• Retrospective cohort (71 CLL & MCL patients median 412d follow-up)
  • 38% minor bleeding (bruising & epistaxis); **18% major bleeding**
  • 10% on CYP3A modifiers => 1/7 major bleed
  • 70% on antiplatelet => 4/50 major bleed
  • 17% on anticoagulant (mostly apixaban for AFib) => 1/12 major bleed
  • 13% on antiplatelet + anticoagulant => **7/9** major bleeding

Kunk, ASH Annual Meeting 2016
Risk Factors of Bleeding

• Prospective cohort study: 85 patients with median follow-up of 24 mo
• 55% developed grade 1-2 bleeding, 0% grade 3-4 bleeding
• Cumulative incidence plateaued at 6 months
• Platelet aggregometry:
  • Baseline impaired platelet aggregation in untreated CLL patients
  • Ibrutinib leads to further impaired collagen but improved ADP activation
• Possible parameters associated with increased risk of low grade bleeding on exploratory analysis (not validated):
  • Longer epinephrine closure $\geq$ 240 sec (HR 2.74)
  • Lower VWF activity $\leq$ 100 IU/dL (HR 2.73)
  • Lower factor VIII $< 174$ IU/dL (HR 3.73)
Suggestions

• Most are not evidence based because there is insufficient data
• Open to group discussion
• Most important question to ask is do we really need ibrutinib if the bleeding risk is high
Suggestion for Antiplatelet on Ibrutinib

• Stop concurrent NSAID, fish oil, vitamin E
• Stop concurrent ASA if low CV risk (primary prophylaxis)
• Use concurrent ASA 81 instead of higher dose if high CV risk (secondary prophylaxis)
• Consider holding ibrutinib if requiring dual antiplatelet therapy (e.g. bare metal stent)
Suggestion for Anticoagulant on Ibrutinib

- Avoid warfarin
- Avoid concurrent antiplatelet and anticoagulant therapy
- FYI: rivaroxaban and apixaban undergo CYP3A4-mediated metabolism (33% & 25%); dabigatran vs. edoxaban do not
- No data on LMWH or DOAC
Suggestion for Bleeding on Ibrutinib

• Non-CNS Bleeding:
  • Hold ibrutinib (partial reversal in 2.5 days)
  • Consider transfusing 1-2U of platelets if immediate hemostasis necessary

• CNS Bleeding:
  • Hold ibrutinib
  • Unclear if platelet transfusion is safe based on extrapolation of data
  • PATCH trial showed that in patients with intraparenchymal hemorrhage while on aspirin, platelet transfusion is associated with higher mortality (OR 2.1, P=0.01)

Baharoglu, Lancet 2016
Suggestion for Procedures on Ibrutinib

- Discuss with primary hematology/oncologist
- Major procedures:
  - Hold for 7 days before procedure
  - Restart 7 days after procedure
- Minor procedures:
  - Hold for 3-7 days before procedure
  - Restart 3-7 day after procedure
Suggestion for AFib on Ibrutinib

• Calculate CHADS2 score:
  • CHF, HTN, Age, Diabetes, Stroke

• Weight risk of stroke vs. bleeding:
  • CHADS2=0, ibrutinib alone
  • CHADS2=1, ibrutinib + ASA 81
  • CHADS2>=2, ibrutinib + DOAC (?apixaban) while avoiding antiplatelet
Future Directions

• Further elucidation of Mechanism
• Prospective cohort studies with long follow-up
• Newer generation BTK inhibitors (weaker TEC inhibition)
• Retrospective population or registry based comparative studies for patients receiving anticoagulant or antiplatelet therapy