Treating T315I-Positive Chronic Myeloid Leukemia (CML)

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Objectives

• Discuss significance of BCR-ABL mutations in CML
• Identify treatment options available for T315I positive CML
• Summarize the data related to each agent’s approval
• Highlight key monitoring parameters and counseling points for these agents

CML

• Caused by expression of BCR-ABL oncoprotein
  ▫ t(9;22)
  ▫ Philadelphia chromosome (Ph+)

• 2014 estimates
  ▫ 5,980 new cases
  ▫ 810 deaths

• Median age at diagnosis: 50-55 years

Treatment Goals

• Maintain remission
• Prevent progression to accelerated phase (AP) or blast phase (BP)
• Minimize therapy-related toxicity

Measuring Treatment Response

Complete Hematologic Response (CHR)

• Complete normalization of peripheral blood counts with leukocyte count <10 cells x10^9/L
• Platelet count <450 cells x10^9/L
• No immature cells in peripheral blood
• No signs/symptoms of disease with disappearance of palpable splenomegaly

Cytogenetic Response

• Complete (CCyR): No Ph-positive metaphases
• Partial (PCyR): 1-35% Ph-positive metaphases
• Major (MCyR): 0-35% Ph-positive metaphases (complete + partial)
• Minor: >35% Ph-positive metaphases

Molecular Response

• Complete: no detectable BCR-ABL mRNA by QPCR (IS)
• Major (MMR):
  ▫ BCR-ABL transcripts 0.1% by QPCR (IS) OR
  ▫ ≥3-log reduction in BCR-ABL mRNA from standardized baseline

Treating CML: A Perspective

1860s
Arsenic

1980s
Interferon-α

1990s
Imatinib

1920s
Splenic Irradiation

1970s Allogeneic Stem Cell Transplant

2000s
Second Generation TKIs

1950s
Busulfan

1960s
Hydroxyurea

2010s
Third Generation TKIs
Tyrosine Kinase Inhibitors (TKIs)

• Bind BCR-ABL ATP-binding site
  ▫ Inhibit cellular growth
  ▫ Induce apoptosis

• 1st line treatment options
  ▫ Imatinib (Gleevec®)
  ▫ Dasatinib (Sprycel®)
  ▫ Nilotinib (Tasigna®)

Drug Resistance in CML

• 20-30% of patients fail to respond to imatinib or experience disease relapse after initial response
  ▫ 37.52% of these patients do not have a response to 2nd generation TKIs

• Classifying resistance
  ▫ Primary (intrinsic)
  ▫ Secondary (acquired)

BCR-ABL Independent Resistance Mechanisms

• Pharmacokinetics and oral bioavailability
  ▫ Variability in drug exposure
  ▫ Variability of CYP450 enzyme system (CYP 3A4)
  ▫ Drug binding (via α1-acid glycoprotein)

• Inadequate intracellular concentrations
  ▫ Concentrations affected by transporters involved in drug influx and efflux

BCR-ABL Independent Resistance Mechanisms

• Activation of alternative signaling pathways
• Clonal evolution
  ▫ Acquisition of additional chromosomal abnormalities
• Stem cell persistence

BCR-ABL Dependent Resistance Mechanisms

• BCR-ABL duplication and amplification
• BCR-ABL kinase domain point mutations
• Mutations outside kinase domain

BCR-ABL Kinase Point Mutations

- Over 100 distinct point mutations identified
- Mutations in kinase domain of BCR-ABL
  - Alter amino acid residues needed for direct contact with TKI
  - Prevent BCR-ABL from assuming the inactive conformation required for imatinib binding


BCR-ABL Kinase Point Mutations

- Frequency increases with sequential TKI therapy
- Mutations may vary by disease phase
  - T315I, E255K/V, Y253F often found in patients with accelerated phase/blast crisis
- Locations
  - Imatinib binding site
  - Phosphate binding (P) loop/ATP binding site
  - Activation (A) loop
  - Catalytic loop


Mutational Analysis

- Direct sequencing (DS)
  - Used by ~80% of laboratories
  - Detects mutations present in ≥20% of Ph+ cells
- Challenges
  - Lack of standardization between laboratories
  - Under-utilization


Timing of Mutational Analysis

NCCN Guidelines

Chronic Phase
- With inadequate initial response, defined as failure to achieve
  - PCyR at 3 and 6 months
  - BCR-ABL/ABL ≤ 10% (IS) at 3 and 6 months
  - CCyR at 12 and 18 months
- Loss of response
  - Hematologic or cytogenetic relapse
  - 1 log increase in BCR-ABL transcript levels and loss of MMR
- Disease progression to AP or BP

NCCN. Chronic Myelogenous Leukemia. V3.2014. Available at:

T315I Mutation

- Accounts for ~14% of detected mutations
- Single nucleotide mutation
  - Threonine to isoleucine substitution at amino acid 315
  - Prevents TKI localization within ATP binding pocket
  - Confers resistance to 1st and 2nd generation TKIs
- Treatment options
  - Ponatinib (Iclusig®)
  - Omacetaxine mepesuccinate (Synribo®)
  - Allogeneic hematopoietic stem cell transplantation (HSCT)

Ponatinib (Iclusig®)

- Granted accelerated approval December 2012
- Pan-BCR-ABL TKI
  - Also inhibits VEGFR, FGFR, PDGFR, EPH and SRC kinases as well as KIT, RET, TIE2 and FLT3

Ponatinib (Iclusig®)

- Initial dose: 45 mg once daily
- Administered without regard to food
- Drug interactions
  - Reduce dose to 30 mg daily when administered with strong CYP3A4 inhibitors
  - Avoid antacids/proton pump inhibitors

Ponatinib Ph+ positive ALL and CML Evaluation (PACE)

- Open-label, multinational phase II trial
- 449 heavily pre-treated patients with CML or Ph-positive ALL
  - Resistant/intolerant to dasatinib or nilotinib
  - Ponatinib 45 mg orally once daily


PACE: Patient Characteristics

- Median age: 59 years (range 18-94)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CP CML (n=270)</th>
<th>AP CML (n=85)</th>
<th>BP CML (n=42)</th>
<th>Ph+ ALL (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous TKI use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>252 (93%)</td>
<td>80 (94%)</td>
<td>59 (95%)</td>
<td>26 (81%)</td>
</tr>
<tr>
<td>≥3</td>
<td>161 (60%)</td>
<td>51 (60%)</td>
<td>37 (60%)</td>
<td>13 (41%)</td>
</tr>
<tr>
<td>Resistance</td>
<td>214 (84%)</td>
<td>74 (92%)</td>
<td>59 (97%)</td>
<td>27 (81%)</td>
</tr>
<tr>
<td>Unacceptable side effects only</td>
<td>40 (16%)</td>
<td>6 (8%)</td>
<td>2 (3%)</td>
<td>2 (7%)</td>
</tr>
</tbody>
</table>


PACE: Efficacy

**Primary Endpoint**
- MCyR
- MaHR
- MMR

**Patients (%):**
- Chronic Phase CML
- Total: Resistant/Intolerant T315I

PACE: Efficacy

Accelerated Phase CML

Blast Phase CML

PACE: Two Year Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>CML-CP</th>
<th>CML-AP</th>
<th>CML-BP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MCyR (%)</td>
<td>CCyR (%)</td>
<td>MMR (%)</td>
</tr>
<tr>
<td>Resistant/Intolerant to dasatinib or nilotinib</td>
<td>56</td>
<td>48</td>
<td>31</td>
</tr>
<tr>
<td>T315I mutation</td>
<td>72</td>
<td>70</td>
<td>58</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>54</td>
<td>38</td>
</tr>
</tbody>
</table>

PACE: Hematologic Toxicity

- Thrombocytopenia (37%)
- Neutropenia (19%)
- Anemia (13%)

PACE: Nonhematologic Toxicity

- Rash
- Dry
- Abdominal pain
- Headache
- Increased lipase
- Constipation
- Fatigue
- Myalgia
- Arthralgia
- Nausea
- Increased ALT
- Hypertension
- Increased AST
- Pancreatitis
- Dyspnea

Ponatinib: Boxed Warnings

- Heart failure
- Hepatotoxicity
  - Liver function tests at baseline, then monthly
- Arterial and venous thrombosis/occlusions
- Myocardial infarction
- Stroke
- Thrombosis
FDA Alert

- October 31, 2013
  - Ponatinib marketing and sales suspended
  - Vascular events
    - Phase 2 trial: 24%
    - Phase 1 trial: 48%
  - May continue in patients responding to therapy and for whom benefits > risks
- December 20, 2013
  - New safety measures implemented

Ponatinib: Safety Measures

- Limited indications
  - Adult patients with T315I-positive CML (CP, AP, or BP) or T315I-positive Ph+ ALL
  - Adult patients with CP, AP, or BP CML or Ph+ ALL for whom no other TKI therapy is indicated
- Revised
  - Warnings and Precautions
  - Dosage and Administration recommendations
  - Patient Medication Guide
  - Iclusig REMS
  - ARIAD’s post market investigations will further evaluate dose selection, drug exposure, treatment response, and toxicity

Ponatinib: Dose Modifications

<table>
<thead>
<tr>
<th>Modification Indication</th>
<th>Laboratory Results</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelosuppression</td>
<td>ANC &lt; 1,000/mm³</td>
<td>1st occurrence: Interrupt ponatinib, resume at 45 mg daily after count recovery (ANC &gt; 1,000/mm³, PLT ≥ 75,000/mm³)</td>
</tr>
<tr>
<td></td>
<td>Platelets &lt; 50,000/mm³</td>
<td>2nd occurrence: Interrupt ponatinib, resume at 30 mg daily dose after count recovery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd occurrence: Interrupt ponatinib, resume at 15 mg daily dose after count recovery</td>
</tr>
</tbody>
</table>

Hepatotoxicity

<table>
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<tr>
<th>Modification Indication</th>
<th>Laboratory Results</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevation AST or ALT &gt; 3 x ULN</td>
<td>Occurrence at 45 mg: Interrupt ponatinib and monitor hepatic function, resume ponatinib at 30 mg after recovery to grade 1 (&lt;3 x ULN)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Occurrence at 30 mg: Interrupt ponatinib and resume at 15 mg after recovery to grade ≤ 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Occurrence at 15 mg: Discontinue ponatinib</td>
<td></td>
</tr>
</tbody>
</table>

Pancreatitis

<table>
<thead>
<tr>
<th>Modification Indication</th>
<th>Laboratory Results</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic grade 1 or 2 elevation of serum lipase</td>
<td>Consider interruption or dose reduction</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic grade 3 or 4 elevation of serum lipase (≥ grade 2)</td>
<td>Discontinue ponatinib</td>
<td></td>
</tr>
<tr>
<td>Symptomatic grade 3 pancreatitis</td>
<td>Occurrence at 45 mg: Interrupt ponatinib and resume at 30 mg after complete resolution of symptoms and recovery of lipase elevation to ≤ grade 1 (&lt;3 x ULN)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Occurrence at 30 mg: Interrupt ponatinib and resume at 15 mg after complete resolution of symptoms and recovery of lipase elevation to ≤ grade 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Occurrence at 15 mg: Discontinue ponatinib</td>
<td></td>
</tr>
</tbody>
</table>

Grade 4 pancreatitis

<table>
<thead>
<tr>
<th>Modification Indication</th>
<th>Laboratory Results</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic grade 4 pancreatitis</td>
<td>Occurrence at 45 mg: Interrupt ponatinib and resume at 30 mg after complete resolution of symptoms and recovery of lipase elevation to ≤ grade 1 (&lt;3 x ULN)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Occurrence at 30 mg: Interrupt ponatinib and resume at 15 mg after complete resolution of symptoms and recovery of lipase elevation to ≤ grade 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Occurrence at 15 mg: Discontinue ponatinib</td>
<td></td>
</tr>
</tbody>
</table>

Omacetaxine Mepesuccinate (Synribo®)

- Granted accelerated approval October 2012
  - CML in CP or AP after failure of 2 or more TKIs
- Synthetic homoharringtonine (HHT)
  - Reversible protein translation inhibitor
  - Inhibition of proteins regulating proliferation and cell growth
  - Induces apoptosis in CML stem cells
  - Provides activity regardless of BCR-ABL mutation status
Omacetaxine Mepesuccinate (Synribo®)

- Dosing
  - Induction
    - 1.25 mg/m² subcut BID x 14 days of 28-day cycle
  - Maintenance
    - 1.25 mg/m² subcut BID x 7 days of 28-day cycle

- Open-label, multinational phase II trials
  - 202: CML with T315I mutation
  - 203: CML resistant and/or intolerant to 2 or more TKIs

- Patient Characteristics
  - Study 202 (n=62)
    - Median age, years (range): 56 (26-83)
    - Number of Prior TKIs, n (%)
      - 1: 16 (26)
      - 2: 30 (48)
      - ≥3: 16 (26)
  - Study 203 (n=46)
    - Median age, years (range): 58 (20-78)
    - Number of Prior TKIs, n (%)
      - 1: 7 (15)
      - 2: 12 (26)
      - ≥3: 27 (59)

- Efficacy
  - Primary endpoint: MHR

- Pooled analysis of Omacetaxine 202 and 203 studies
  - Primary endpoint: MHR

- Patients in advanced phase CML
  - CML 202 (n=20)
  - CML 203 (n=31)

- Pooled Analysis: Efficacy
  - Response | AP (%) | BP (%)
  - MHR      | 37     | 4
  - MCyR     | 3      | 0
  - MHR (Patients with T315I) | 55 | 10
CML 202/203: Hematologic Toxicity

<table>
<thead>
<tr>
<th>Toxicity (all grades)</th>
<th>CML 202 (%)</th>
<th>CML 203 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>79</td>
<td>67</td>
</tr>
<tr>
<td>Anemia</td>
<td>66</td>
<td>54</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>18</td>
<td>-</td>
</tr>
</tbody>
</table>

CML 202/203: Nonhematologic Toxicity

<table>
<thead>
<tr>
<th>Toxicity (all grades)</th>
<th>CML 202 (%)</th>
<th>CML 203 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>40</td>
<td>44</td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td>Headache</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Asthenia</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Vomiting</td>
<td>-</td>
<td>15</td>
</tr>
</tbody>
</table>

Omacetaxine: Dose Modifications

<table>
<thead>
<tr>
<th>Modification</th>
<th>Indication</th>
<th>Laboratory Results</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelosuppression</td>
<td>ANC &lt; 500/mm³ or Platelets &lt; 50,000/mm³</td>
<td>Delay start of next cycle until ANC &gt; 1000 and platelets ≥ 50,000 AND reduce number of treatment days by 2 days</td>
<td></td>
</tr>
<tr>
<td>Nonhematologic Toxicity</td>
<td>Manage symptomatically and interrupt/delay treatment until toxicity resolves</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Allogeneic HSCT

- Remains only curative therapy
- NCCN recommendations
  - BP at diagnosis
  - T315I/other BCR-ABL mutations resistant to TKIs
  - Intolerance to all TKIs
- 5-year survival rates following matched-related HSCT
  - CP: 75%
  - AP: 40%
  - BP: 10%

Future Directions...

- TKIs
  - XL228
    - Potent multi-target kinase inhibitor
  - Rebastinib (DCC-2036)
  - Switch control inhibitor
  - Induces/stabilizes inactive ABL conformation
  - Aurora Kinase Inhibitors
    - Danusertib
      - Activity against all known aurora kinases in addition to BCR-ABL tyrosine kinase
Question 1
- When given concomitantly with strong CYP3A4 inhibitors, ponatinib should initially be dosed at 15 mg by mouth daily
  A. True
  B. False

Question 2
- BCR-ABL mutational analysis testing is appropriate when
  A. Patients fail to achieve adequate initial response
  B. Patients lose response to therapy
  C. Patients progress to accelerated phase or blast phase
  D. All of the above

Question 3
- Patients receiving omacetaxine mepesuccinate are transitioned to maintenance dosing once a hematologic response is achieved
  A. True
  B. False

Questions?
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