Chronic Myeloid Leukemia
Updates on recent clinical papers

Ng Vin Cci, BSc(Pharm)(Hons), BCOP Pharmacist
Singapore General Hospital
7th July 2010

Overview

- CML background
- 2009 European LeukemiaNet Guidelines
- Updated data from ENEST and DASISION trials

Chronic Myeloid Leukemia

- Clonal myeloproliferative disorder of pluripotent stem cells
- Increase proliferation, decrease apoptosis
- Cytogenetic hallmark: Ph chromosome
- Molecular hallmark: Bcr-Abl; Bcr-Abl initiation causal event in CML
- Epidemiology
  - Median age – 45 to 55 years old
  - 15 – 20% of all leukemias in adults

CML – Disease Course

<table>
<thead>
<tr>
<th>Chronic Phase</th>
<th>Progressive Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median 5 - 6 years stabilization</td>
<td>Median duration 6 – 9 months</td>
</tr>
<tr>
<td>Median survival 3 – 6 months</td>
<td></td>
</tr>
</tbody>
</table>

Historical versus Current Perspective

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Historical (until 2000)</th>
<th>Current (since 2000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Course</td>
<td>Fatal</td>
<td>Indolent</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Poor</td>
<td>Excellent</td>
</tr>
<tr>
<td>Median survival, yrs</td>
<td>3 - 6</td>
<td>≥ 25</td>
</tr>
<tr>
<td>Frontline treatment</td>
<td>Allogenic SCT, interferon alfa, hydroxyurea</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Second-line treatments</td>
<td>Not established</td>
<td>Allogenic SCT, novel TKIs</td>
</tr>
</tbody>
</table>

Imatinib: IRIS 8-year Update

- IRIS established imatinib as standard initial therapy for chronic phase CML.
- 8-year update of IRIS
  - 354 of 553 (55%) remained on study, 98.4% of these patients were on imatinib, 1.6% remained on IFN/Ara-C
  - No new safety issue identified
  - Estimated EFS at 8 years = 81%
  - Estimated rate without AP/BC at 8 years = 92%
  - Overall survival (ITT) = 85%, Survival: Death associated with CML = 93%
European LeukemiaNet (ELN)
CML Guidelines 2009
An update from the 2006 ELN CML Guidelines

ELN 2009: Definition of Response and Monitoring

**Hematological Response**
*Complete* CHR
- Platelet count < 450 x 10^9/L
- WBC count < 10 x 10^9/L
- Differential w/o immature granulocytes & < 5% basophils
- Non-palpable spleen

**Cytogenetic Response**
*Complete* (CCyR): Ph+ none
*Partial* (PCyR): Ph+ 1 – 35%
*Minor*: Ph+ 36 – 65%
*Minimal*: Ph+ 66 – 95%
*None*: Ph+ > 95%

**Molecular Response**
*Complete*: transcript non-detectable
*Major (MMR)*: ≤ 0.1%

**Monitoring**
- Check at diagnosis, then q2w until complete response achieved & confirmed, then q3m unless otherwise specified
- RT-Q-PCR: Check q3m, then at least q6m
- Mutational analysis only in case of failure, suboptimal response or increased level of transcript

---

**ELN 2009: Classification of Responses**

<table>
<thead>
<tr>
<th>Months</th>
<th>Optimal response</th>
<th>Suboptimal response</th>
<th>Failure</th>
<th>Warning</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>CHR &amp; at least minor CyR</td>
<td>No CyR</td>
<td>&lt; CHR</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>At least PCyR</td>
<td>&lt; PCyR</td>
<td>No CyR</td>
<td>NA</td>
</tr>
<tr>
<td>12</td>
<td>CCyR</td>
<td>PCyR</td>
<td>&lt; PCyR</td>
<td>&lt; MMR</td>
</tr>
<tr>
<td>18</td>
<td>MMR</td>
<td>&lt; MMR</td>
<td>No CyR</td>
<td>NA</td>
</tr>
<tr>
<td>Anytime</td>
<td>Stable or improving MMR</td>
<td>Loss of MMR Low IM IC50 mutations</td>
<td>Loss of CHR Low IM IC50 mutations Ph+ CCA</td>
<td>Any rise in transcript levels Ph-CCA</td>
</tr>
</tbody>
</table>

Summary of ELN Treatment Recommendations 2009

<table>
<thead>
<tr>
<th>Response</th>
<th>Second-line</th>
<th>Third line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intolerance</td>
<td>Nilotinib, Dasatinib</td>
<td></td>
</tr>
<tr>
<td>Suboptimal response</td>
<td>Imatinib 600 or 800 mg QD Nilotinib, Dasatinib Check compliance</td>
<td>Continue nilotinib, dasatinib AplHST if warning (prior hematologic resistance, mutations) EBMT risk&lt;2</td>
</tr>
<tr>
<td>Failure</td>
<td>Nilotinib, Dasatinib or alloHSTC in pts in progression or with T315I mutation Check compliance</td>
<td>AplHSTC</td>
</tr>
<tr>
<td>Warnings</td>
<td>Continue Imatinib 400 mg/d Observe Check compliance</td>
<td></td>
</tr>
</tbody>
</table>

Summary of ELN Treatment Recommendations 2009

- Imatinib dose escalation is an option in suboptimal response but is no longer recommended after failure of response
- 2nd line treatment: high dose imatinib, nilotinib or dasatinib in all patients
- Provisional definition of response to 2nd generation TKIs introduced
ELN 2009: Allogeneic HSCT in CML

At Diagnosis (Front-line)

In pts presenting in AP or BP
Pretreatment with a TKI recommended

Imatinib failure
In pts who have already progressed to AP or BP
Pretreatment with 2nd generation TKI is recommended
In patients with T315I mutation

Imatinib failure OR
Suboptimal response to 2nd generation TKIs (2nd line)
In all eligible pts, depending on response and on EBMT risk score


Nilotinib Demonstrates Superior Efficacy compared with Imatinib in patients with Newly diagnosed CML-CP: Results From the International Randomized Phase III ENESTnd Trial

Giuseppe Saglio, Dong-Wook Kim, Surapol Issaragrisil, Philipp le Coutre, Joey Reiffers, Christian Lubin, Ricardo Pazdur, Richard Clark, Timothy Hughes, Andreas Hochhaus, Neil Gallagher, Albert Hoenekopp, Mei Dong, Ariful Haque, Hagop Kantarjian and Richard Larson

Study design and Endpoints

N = 846
(217 centers, 35 countries)
Randomized, follow-up 5 years

Stratified by Sokal risk score

- Primary endpoint: MMR at 12 months
- Secondary endpoint: CCyR by 12 months
- Other endpoints: Time to and duration of MMR and CCyR, EFS, PFS, time to AP/blast, OS

ENESTnd: Primary Endpoint (MMR rate at 12 Mos)

N = 846
(217 centers, 35 countries)
Randomized, follow-up 5 years

Stratified by Sokal risk score

- Primary endpoint: MMR at 12 months
- Secondary endpoint: CCyR by 12 months
- Other endpoints: Time to and duration of MMR and CCyR, EFS, PFS, time to AP/blast, OS

ENESTnd: CCyR Rates by 12 Mos and Overall

- Among patients who had cytogenetic assessment at 18 mos (n = 442/846), the rates of CCyR were
  - Nilotinib 300 mg BID 99%
  - Nilotinib 400 mg BID 99%
  - Imatinib 89%

- Overall progression to AP/BC
  - Nilotinib 300 mg BID 0.7%
  - Nilotinib 400 mg BID 0.4%
  - Imatinib 4.2%

ENESTnd: Grade 3/4 Myelosuppression
ENESTnd: Key Summary

- Nilotinib is superior to imatinib with significantly higher rates of MMR and CCyR, at both 300 mg BID and 400 mg BID
- Significantly fewer patients on nilotinib progressed compared to imatinib
- Nilotinib is superior to imatinib across all Sokal risk groups, generally more tolerable
- Incidence of AEs leading to discontinuation was lowest in the nilotinib 300 mg BID arm (Grade 3/4 46% vs 52%)
- Based on these results nilotinib may become the new standard of care in newly diagnosed CML

Dasatinib versus Imatinib in Newly Diagnosed Chronic-Phase CML: A Randomized Phase III Trial

The DASISION Study


Study design and Endpoints

N = 519 (108 centers, 26 countries) Randomized, follow-up 5 years

- Primary endpoint: CCyR at 12 months
- Secondary endpoint: CCyR no Ph+ metaphases in BM, MMR
- Other endpoints: Time to MMR and CCyR, PFS, DS

Stratified by Hasford risk score

DASISION: Primary Endpoint (CCyR rate by 12 mo)

DASISION: Key Summary

- Dasatinib associated with superior efficacy compared to imatinib as 1st line treatment of CP-CML
- Higher and faster rates of CCyR, confirmed CCyR and MMR
- Dasatinib generally well tolerated
- Low rates of grade 3/4 hematologic toxicity
- Pleural effusion (10%) more frequent in dasatinib (92% with PE achieved 12mo CCyR, 1.2% stopped treatment)
- Results support use of dasatinib as 1st line therapy patients with newly diagnosed CP-CML
### Special Considerations

- **Adverse events specific to TKIs:**
  - Imatinib: Edema (periorbital) and muscle cramps
  - Dasatinib: Pleural effusion (5% w. once a day dosing), thrombocytopenia
  - Nilotinib: Liver enzymes elevations, QTc prolongation, elevation of lipase

- **Mutational analysis in guiding choice of TKIs**
  - Dasatinib: Y253F/H, E255K/V, F359C/I
  - Nilotinib: V299L, F317L/V
  - Clinical trial e.g. AP24534, HHT, LBH589, AlloHSCT (T315I)

- **Increasing resistance to TKIs**

- **Potential drug interactions (major CYP3A4 substrates), food-drug interactions (nilotinib to be taken on empty stomach)**

---

Sources:
- Sawyer LC, N Engl J Med 2010
- Burgess et al, PNAS, 2005
- Bradeen et al, Blood 2006