Taiwan Guidelines for the Management of Chronic Myeloid Leukemia

Taiwan CML Study Group

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Contents

• Initial work-up at diagnosis and define baseline prognostic factors and disease phase

• Treatment recommendations for different phases of disease

• Definitions of hematologic, cytogenetic and molecular responses to TKIs treatment

• Recommendations of cytogenetic/molecular monitoring and mutational analysis

• Treatment landmarks evaluation and decision makings

• Issues of hematopoietic stem cell transplantation

• Overview of side effects, drug interactions, specific non-hematologic toxicities for different TKIs, and management of adverse effects
Initial Evaluation for CML

- History taking and physical examination
  - Spleen size by palpation (cm below costal margin)
- CBC, DC, and platelets
- Chemistry profile
- Leukocyte alkaline phosphatase score
- Bone marrow aspirate and biopsy
  - Cytogenetics (BM)
- RT-PCR (PB) and baseline RQ-PCR if BCR-ABL1 (+)
- Sokal score

Ph(-) and BCR-ABL1 (-)
- Evaluate for other disease (not CML)

Ph (+) and/or Ph (-)/BCR-ABL1 (+)
- CML treatment guidelines
Careful Clinical Supervision

• Particular attention should be given to the risk of myelosuppression and tumor lysis syndrome, and also to elderly patients and those with pre-existing cardiac disease.

• Baseline assessment of complete blood count and biochemistry profile
  - weekly for the first 4 weeks
  - every 2 weeks until 12 weeks of therapy
  - then every 4 weeks
  - check-up by physician’s decision after MMR achievement

• ECG, echocardiography and/or pulmonary function tests, if risk factors for cardiovascular and/or respiratory dysfunction
Baseline Prognostic Factors

- Prognostic systems
  - Sokal score
  - EUTOS score: $7 \times \text{basophils (\%)} + \text{spleen size (cm)}$
    - ELN recommends dividing patients into low ($\leq 87$) and high-risk ($>87$) groups.

- Clonal chromosomal abnormalities (CCA)/Ph+ have been reported to have an adverse prognostic value, particularly in the so called “major route” abnormalities
  - Extra Ph, +8, +19, and iso17.
  - Chromosome 9 deletions and variant translocations have no value for prognosis.
## Calculation and Definition of Sokal Risk Score

<table>
<thead>
<tr>
<th></th>
<th>Sokal score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>$0.0116 \times (\text{age} - 43.4)$</td>
</tr>
<tr>
<td><strong>Spleen (cm below costal margin, maximum distance)</strong></td>
<td>$0.0345 \times (\text{spleen} - 7.51)$</td>
</tr>
<tr>
<td><strong>Platelet count, x 10^9/L</strong></td>
<td>$0.188 \times [(\text{platelet count} \div 700)^2 - 0.563]$</td>
</tr>
<tr>
<td><strong>Blood myeloblasts, %</strong></td>
<td>$0.0887 \times (\text{myeloblasts} - 2.10)$</td>
</tr>
<tr>
<td><strong>Relative risk</strong></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>$&lt; 0.8$</td>
</tr>
<tr>
<td>Intermediate</td>
<td>$0.8 - 1.2$</td>
</tr>
<tr>
<td>High</td>
<td>$&gt; 1.2$</td>
</tr>
</tbody>
</table>

Calculation of the risk requires use of clinical and hematologic data at diagnosis, prior to any treatment.

http://www.leukemia-net.org/content/leukemias/cml/cml_score/index_eng.html

* $\text{Exp} \ 0.0116 \times (\text{age in years} - 43.4) + 0.0345 \times (\text{spleen} - 7.51) + 0.188 \times [(\text{platelet count} \div 700)^2 - 0.563] + 0.0887 \times (\text{blast cells} - 2.10)$
Can Baseline Prognostic Factors Provide A Guide to Treatment?

**Not Yet!**

<table>
<thead>
<tr>
<th>Warning</th>
</tr>
</thead>
<tbody>
<tr>
<td>-High risk score (Sokal or EUTOS)</td>
</tr>
<tr>
<td>-Clonal chromosomal abnormalities (CCA) in Ph+ cells, “major route”: extra Ph, +8, +19, and iso(17q)</td>
</tr>
</tbody>
</table>

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Additional Clonal Cytogenetic Abnormalities Emerging on TKIs Therapy

- Clonal cytogenetic evolution
  - Additional clonal chromosomal abnormalities in Ph+ cells (CCA/Ph+)
  - CCA/Ph+ defines TKI failure
- CCA/Ph+ is associated with shorter OS on second-line imatinib (after IFNα failure), but not second-line dasatinib or nilotinib.

- Clonal cytogenetic abnormalities in Ph- cells occur in 5-10% of patients and, in the absence of dysplasia, do not seem to adversely affect outcome. The exception are abnormalities of chromosome 7 [monosomy 7 and del(7q)], which indicate a risk of myelodysplasia and acute leukemia, and justify long-term follow-up bone marrow biopsies.

- Other patients with CCA/Ph- require marrow examination only in case of cytopenias or dysplastic peripheral blood morphology.
# Accelerated Phase – Criteria (Anyone)

<table>
<thead>
<tr>
<th>WHO criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blast cells in blood or BM 10%-19%; or blasts plus promyelocytes in</td>
</tr>
<tr>
<td>blood or BM &gt; 30% with blasts &lt; 20%</td>
</tr>
<tr>
<td>Basophils in blood ≥ 20%</td>
</tr>
<tr>
<td>Persistent thrombocytopenia (&lt; 100 x 10⁹/L) unrelated to therapy</td>
</tr>
<tr>
<td>Thrombocytosis (&gt; 1000 x 10⁹/L) unresponsive to therapy</td>
</tr>
<tr>
<td>Clonal chromosomal abnormalities in Ph + cells (CCA/Ph+, on treatment)</td>
</tr>
<tr>
<td>Increasing spleen size and increasing WBC count unresponsive to therapy</td>
</tr>
</tbody>
</table>
### Blastic Phase – Criteria (Anyone)

<table>
<thead>
<tr>
<th>WHO criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blasts in PB or BM $\geq 20%$</td>
</tr>
<tr>
<td>Extramedullary blast proliferation</td>
</tr>
<tr>
<td>Large foci or clusters of blasts in bone marrow biopsy</td>
</tr>
</tbody>
</table>
Treatment Recommendations for CML in Chronic Phase

- First line treatment (in chronic phase)
  - Imatinib 400mg
  - Nilotinib 300mg BID
  - Dasatinib 100mg QD
    - Must ensure patient’s compliance.
    - Anti-hyperuricemic drugs should be given for patients with high tumor burden.

- The three TKIs can be used also in second or subsequent lines, at the standard or at a higher dose (600 mg once daily for imatinib, 400 mg twice daily for nilotinib, and 70 mg twice daily or 140 mg once daily for dasatinib).

- Hydroxyurea can be used until the diagnosis of CML has been confirmed. IFNα alone is recommended only in the rare circumstances where a TKI cannot be used. Cytotoxic chemotherapy is never recommended in CP.
## Treatment Recommendations for CML in AP or BP

| AP and BP in newly diagnosed patients (TKI naïve) | Imatinib: 600mg QD for AP patients; 400 mg twice daily for BP patients.  
Nilotinib 400mg BID for AP patients.  
Dasatinib: 140 mg once daily for both AP and BP patients.  
Stem cell donor search.  
Then, alloSCT is recommended for all BP patients and for the AP* patients who do not achieve an optimal response.  
Chemotherapy may be required before alloSCT, to control the disease. |
|---|---|
| AP and BP patients progressed from CP (TKI pretreated) | Anyone of the TKIs that were not used before progression (ponatinib in case of T315I mutation), then alloSCT in all patients.  
Chemotherapy is frequently required to make patients eligible to alloSCT. |

- In TKI naïve patients, AP is believed to be close to high risk CP, so that TKIs have priority.
- In patients who progress to AP or BP during TKI therapy, the response to any subsequent treatment is poorer, so that alloSCT is recommended for all the patients who are eligible to the procedure.
- AlloSCT is not recommended in patients with uncontrolled and resistant BP.
- Nilotinib was tested, but was not approved for the treatment of BP.

*Baccarani et al, Blood 2013; 122: 885*
Treatment Recommendations of Advanced Phase

- BM cytogenetics
- Mutational analysis (in TKI pretreated pts)

- Imatinib 600mg QD, nilotinib 400mg BID (only for AP patients), or dasatinib 140 mg QD
- Stem cell donor search and consider HSCT based on response
- Clinical trial

- ALL-type induction chemotherapy + TKI followed by HSCT if feasible
- TKI followed by HSCT if feasible
- Clinical trial

- AML-type induction chemotherapy + TKI followed by HSCT if feasible
- TKI followed by HSCT if feasible
- Clinical trial

Accelerated phase

Advanced phase

Blast phase

- BM cytogenetics
- Acute leukemia study (flow cytometry, cytochemistry, etc.)
- Mutational analysis (in TKI pretreated pts)

Lymphoid

Myeloid
Definition of Hematologic and Cytogenetic Responses

<table>
<thead>
<tr>
<th>Response by Type</th>
<th>Definition</th>
</tr>
</thead>
</table>
| Hematologic response Complete (CHR) | • WBC < 10 x10^9/L  
• Basophils < 5%  
• No myelocytes, promyelocytes, myeloblasts in PB  
• Platelet count < 450 x10^9/L  
• No signs and symptoms of disease with disappearance of palpable splenomegaly |
| Cytogenetic response Complete (CCyR) | ➢ No Ph metaphases |
| Partial (PCyR) | ➢ 1% to 35% Ph metaphases |
| Minor (mCyR) | ➢ 36% to 65% Ph metaphases |
| Minimal (minCyR) | ➢ 66% to 95% Ph metaphases |
| None (noCyR) | ➢ > 95% Ph metaphases |

• Only chromosome banding analysis (CBA) of marrow cell metaphases can be used to assess the degree of CyR, with at least 20 metaphases analyzed  
• FISH of blood interphase cell nuclei could be substituted for CBA of marrow cell metaphases only for the assessment of CCyR, which is then defined by less than 1% \textit{BCR-ABL1} positive nuclei out of at least 200 nuclei.
Definition of Deep Molecular Responses

MR⁴ (≧ 4 log reduction; ≦ 0.01%IS)

MR⁴.⁵ (≧ 4.5 log reduction; ≦ 0.0032%IS)

MR⁵ (≧ 5 log reduction; ≦ 0.001%IS)

log reduction = reduction from IRIS baseline, not individual pretreatment levels

Cross et al. Leukemia. 2012.
## Definition of Molecular Responses

<table>
<thead>
<tr>
<th>Molecular response</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major MR (MMR)*</td>
<td>- <em>BCR-ABL1</em> expression (IS) ≤ 0.1%</td>
</tr>
<tr>
<td>MR(^{4.0})</td>
<td>- Detectable disease with &lt;0.01% <em>BCR-ABL1</em> IS or&lt;br&gt;- Undetectable disease in cDNA with &gt;10,000 <em>ABL1</em> transcripts</td>
</tr>
<tr>
<td>MR(^{4.5})</td>
<td>- Detectable disease with &lt;0.0032% <em>BCR-ABL1</em> IS or&lt;br&gt;- Undetectable disease in cDNA with &gt;32,000 <em>ABL1</em> transcripts</td>
</tr>
<tr>
<td>Molecularly undetectable leukemia (previous CMR)</td>
<td>- molecularly undetectable leukemia</td>
</tr>
</tbody>
</table>

* MMR should be confirmed in two subsequent occasions one month apart.

*Baccarani et al, Blood 2013; 122: 885*
Recommendations for Monitoring

**Hematologic response**
- weekly until CHR

**Cytogenetic response (BM)**
- 6-monthly until CCyR*
  
  If adequate molecular monitoring can be ensured, cytogenetics can be spared.
  
  **Molecular response (PB)**
- 3-6 monthly
  
  * Q 3 months before MMR, Q 3-6 months after MMR
Response to Treatment - ELN 2013

No recommendation which TKI should be used, but which response should be achieved, irrespective of any TKI that is used.

• **Optimal:** There is no indication that a change of therapy may significantly improve outcome.

• **Failure:** The risk of progression and death from leukemia is significant. The patient should receive a different treatment, whenever available and applicable.

• **Warning** (previously sub-optimal): The characteristics of the disease and the response to treatment require more careful and more frequent monitoring, and a mutational analysis.
## ELN Definition of The Response to First-Line TKIs (Any TKI)

<table>
<thead>
<tr>
<th></th>
<th>Optimal</th>
<th>Warning</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>NA</td>
<td>- High risk or</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- CCA/Ph+, major route</td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>$BCR-ABL1 \leq 10%,$</td>
<td>$BCR-ABL1 &gt; 10%,$</td>
<td>No CHR, and/or</td>
</tr>
<tr>
<td></td>
<td>and/or Ph+ $\leq 35%$</td>
<td>and/or $Ph+ 36%-95%$</td>
<td>Ph+ $&gt; 95%$</td>
</tr>
<tr>
<td>6 mo</td>
<td>$BCR-ABL1 \leq 1%,$</td>
<td>$BCR-ABL1 1%-10%$</td>
<td>$BCR-ABL1 &gt; 10%,$</td>
</tr>
<tr>
<td></td>
<td>and/or Ph+ 0</td>
<td>and/or $Ph+ 1%-35%$</td>
<td>and/or $Ph+ &gt; 35%$</td>
</tr>
<tr>
<td>12 mo</td>
<td>$BCR-ABL1 \leq 0.1%$</td>
<td>$BCR-ABL1 0.1%-1%$</td>
<td>$BCR-ABL1 &gt; 1%$ (repeat at 13 mo), and/or</td>
</tr>
<tr>
<td>Then</td>
<td></td>
<td></td>
<td>Ph+ $&gt; 0%$</td>
</tr>
<tr>
<td></td>
<td>$BCR-ABL1 \leq 0.1%$</td>
<td>CCA/Ph- (-7 or 7q-)</td>
<td>- Loss of CHR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Loss of CCyR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Confirmed loss of MMR (MR$^{3.0}$): in two</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>consecutive tests, of which one with a $BCR$-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$ABL1$ transcript level $\geq 1%$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Mutations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- CCA/Ph+</td>
</tr>
</tbody>
</table>

- apply also to second line treatment, when first line treatment was changed for intolerance.
- After 12 months, if an MMR is achieved, the response can be assessed by RQ-PCR every 3 to 6 months, and cytogenetics is required only in case of failure, a time of rising 10x of $BCR-ABL1$ transcript without an MMR or if standardized molecular testing is not available.
- Notice that MMR (MR$^{3.0}$ or better) is optimal for survival, but that a deeper response is likely to be required for a successful discontinuation of treatment.
## ELN: Optimal Response

<table>
<thead>
<tr>
<th>Time</th>
<th>2009(^1)</th>
<th>2013(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>- CHR, and</td>
<td>- CHR, and</td>
</tr>
<tr>
<td></td>
<td>- at least minor CyR (Ph+ ≤ 65%)</td>
<td>- at least PCyR (Ph+ ≤ 35%), and/or BCR-ABL1 ≤ 10%</td>
</tr>
<tr>
<td>6 months</td>
<td>- at least PCyR (Ph+ &lt;35%)</td>
<td>- CCyR (Ph+ 0), and/or BCR-ABL1 &lt;1%</td>
</tr>
<tr>
<td>12 months</td>
<td>- CCyR (Ph+ 0)</td>
<td>- MMR (BCR-ABL1 ≤ 0.1%)</td>
</tr>
<tr>
<td>Then</td>
<td>- MMR (BCR-ABL1 ≤ 0.1%) or better</td>
<td>- MMR (BCR-ABL1 ≤ 0.1%) or better</td>
</tr>
</tbody>
</table>

\(^1\)Baccarani et al, JCO 2009; 27: 6041  
\(^2\)Baccarani et al, Blood 2013; 122: 885
Failures

• **Primary failure** (failure to achieve a given response at a given time)
  - Plasma levels
  - Drug Pumps
  - Low levels of normal HSC

• **Secondary failure** (loss of response)
  - *BCR-ABL1* kinase domain mutation
  - *BCR-ABL1* gene amplification
  - CCA/Ph+
  - *BCR-ABL1* independent mechanisms
    
    *(Hamilton A et al. Blood 2012)*
# Failure (ELN Criteria)

## Primary failure

<table>
<thead>
<tr>
<th>Time</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mo</td>
<td>No CHR, and/or No CyR (Ph+ &gt; 95%)</td>
</tr>
<tr>
<td>6 mo</td>
<td>BCR-ABL1 &gt;10%, and/or less than PCyR (Ph+ &gt;35%)</td>
</tr>
<tr>
<td>12 mo</td>
<td>BCR-ABL1 &gt;1%, and/or less than CCyR</td>
</tr>
</tbody>
</table>

## Secondary failure

- Loss of CHR - Loss of CCyR
- All mutations - CCA / Ph+
- Confirmed loss of MMR in two consecutive tests >0.1%, of which one must be > 1%

*Baccarani et al, Blood 2013; 122: 885*
## Definitions of The Response to 2nd Line Therapy (Nilotinib or Dasatinib) in Imatinib Failure Cases

<table>
<thead>
<tr>
<th></th>
<th>Optimal</th>
<th>Warning</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>NA</td>
<td>- No CHR or</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Loss of CHR or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Lack of CyR or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- High risk</td>
<td></td>
</tr>
<tr>
<td><strong>3 mo</strong></td>
<td>- <em>BCR-ABL1</em> ≤ 10%</td>
<td>- <em>BCR-ABL1</em> &gt; 10%</td>
<td>- No CHR</td>
</tr>
<tr>
<td></td>
<td>- Ph+ &lt; 65%</td>
<td>- Ph+ 65-95%</td>
<td>- Ph+ &gt; 95%,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- New mutations</td>
</tr>
<tr>
<td><strong>6 mo</strong></td>
<td><em>BCR-ABL1</em> ≤ 10%, and/or Ph+ &lt; 35%</td>
<td><em>BCR-ABL1</em> &gt; 10% and Ph+ 35-65%</td>
<td>- <em>BCR-ABL1</em> &gt; 10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Ph+ &gt; 65%,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- New mutations</td>
</tr>
<tr>
<td><strong>12 mo</strong></td>
<td><em>BCR-ABL1</em> &lt; 1%, and/or Ph+ 0%</td>
<td><em>BCR-ABL1</em> 1-10%</td>
<td>- <em>BCR-ABL1</em> &gt; 10%, and/or Ph+ &gt; 35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Ph+ 1-35%</td>
<td>- New mutations</td>
</tr>
<tr>
<td><strong>Then</strong></td>
<td><em>BCR-ABL1</em> ≤ 0.1%</td>
<td>- CCA/Ph- (-7 or 7q-)</td>
<td>- Loss of CHR,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- <em>BCR-ABL1</em> &gt; 0.1%</td>
<td>- Loss of CCyR or PCyR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- New mutations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Confirmed loss of MMR (MR^3.0) in two consecutive tests, of which one with a <em>BCR-ABL1</em> transcript level ≥ 1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- CCA/Ph+</td>
</tr>
</tbody>
</table>
## Recommendations for Tests at Diagnosis And Monitoring Following Treatment

<table>
<thead>
<tr>
<th>At diagnosis</th>
<th>During treatment</th>
<th>Failure/progression</th>
<th>Warning</th>
</tr>
</thead>
</table>
| • Chromosome banding analysis (CBA) of marrow cell metaphases  
• FISH in case of Ph negativity to identify variant or cryptic translocations  
• RT-PCR to identify transcript type | • RQ-PCR for the determination of $BCR-ABL1$ transcripts on IS every 3 months until an MMR, then every 3 to 6 months, and/or  
• CBA of marrow cell metaphases (performed at 3, 6, and 12 months until a CCyR achieved, then every 12 months. Once a CCyR is achieved, FISH on blood cells can be done. | • RQ-PCR  
• Mutational analysis  
• CBA of marrow cell metaphases  
• Immunophenotyping in BP | Molecular and cytogenetic tests to be performed more frequently.  
• CBA of marrow cell metaphases recommended in case of myelodysplasia or CCA/Ph- with chromosome 7 involvement. |

*Baccarani et al, Blood 2013; 122: 885*
**Chronic Phase, Treatment Recommendations for 1\textsuperscript{st}, 2\textsuperscript{nd} And Subsequent Lines of Treatment**

<table>
<thead>
<tr>
<th>Line</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| 1\textsuperscript{st} line | Imatinib, or nilotinib, or Dasatinib  
HLA type patients and siblings only in case of baseline warnings (high risk, major route CCA/Ph+) |
| 2\textsuperscript{nd} line, intolerance to the first TKI | Anyone of the other TKIs approved first-line (imatinib, nilotinib, dasatinib) |
| 2\textsuperscript{nd} line, failure of imatinib first-line | Dasatinib, or nilotinib  
HLA type patients and siblings. |
| 2\textsuperscript{nd} line, failure of nilotinib first-line | Dasatinib  
HLA type patients and siblings, search for an unrelated stem cell donor, consider alloSCT |
| 2\textsuperscript{nd} line, failure of dasatinib first-line | Nilotinib  
HLA type patients and siblings, search for an unrelated stem cell donor, consider alloSCT |
| 3\textsuperscript{rd} line, failure of, or/and intolerance to, two TKIs | Anyone of the remaining TKIs. AlloSCT recommended in all eligible patients |
| Any line, T315I mutation | HLA type patients and siblings, search for an unrelated stem cell donor, consider alloSCT |

*Baccarani et al. Blood, ELN 2013*
Therapy According to Response

Optimal response
- Maintain current medication and dose
- Molecular monitoring every 3 months
- Molecular monitoring every 3-6 months if MMR achieves

Failure
- Change to alternative TKI (if mutation (+), according to mutation profile)
- Increase current dose (only for first-line nilotinib and dasatinib, not for imatinib)
- Evaluation of HSCT depending on response to 2nd or 3rd line TKIs

Warning
- Keep or increase current dose
- Change to alternative TKI (if mutation (+), according to mutation profile)
- More frequent RQ-PCR monitoring (even monthly)
Flow Chart in Failure/Warning Response

- Investigation
  - Ensure Compliance
    - BM exam and cytogenetics
  - Drug Interaction?
    - FISH BCR-ABL amplification
    - Mutational Analysis
Indication of Mutational Analysis

• Chronic phase
  ➢ Failure defined at different time points
  ➢ Any time: loss of CHR, CCyR, or MMR,
  ➢ \( BCR-ABL1 \) increase > 10 X

• Disease progression to AP or BP
At 3 Months

Optimal: 

**BCR-ABL1 ≤ 10%**

and/or PCyR

Continue current dose of TKI

Monitor RQ-PCR Q3M

- Change to alternative TKI (if mutation (+), according to mutation profile)
- Increase imatinib to 800mg, as tolerated (if not candidate of alternative TKI)
- Same dose or increase current dose (for nilotinib and dasatinib)
- Evaluation of HSCT depending on response to 2nd line TKIs

Warning:

- Keep or increase current dose
- Change to alternative TKI (if mutation (+), according to mutation profile)
- More frequent RQ-PCR monitoring (even monthly)

Failure:

No CHR, and/or Ph+ > 95%

- Check compliance
- Drug - drug interactions
- Mutational analysis

3 M evaluation

Warning:

**BCR-ABL1 > 10%**, and/or Ph+ 36-95%

- Check compliance
- Drug - drug interactions
- Mutational analysis
At 6 Months

Optimal: $BCR-ABL1 \leq 1\%$, and/or Ph + 0

Continue current dose of TKI

Monitor RQ-PCR Q3M

Failure: $BCR-ABL1 > 10\%$, and/or Ph + > 35%

- Check compliance
- Drug - drug interactions
- Mutational analysis

- Change to alternative TKI (if mutation (+), according to mutation profile)
- Same dose or increase current dose (for nilotinib and dasatinib)
- Evaluation of HSCT depending on response to 2nd line TKIs

Warning: $BCR-ABL1$ 1-10\% and/or Ph + 1-35%

- Keep or increase current dose
- Change to alternative TKI (if mutation (+), according to mutation profile)
- More frequent RQ-PCR monitoring (even monthly)

6M evaluation
At 12 Months

12 M evaluation

Optimal: $BCR-ABL1 \leq 0.1\%$
Continue current dose of TKI
Monitor RQ-PCR Q3-6M

12 M evaluation

Failure: $BCR-ABL1 > 1\%$, and/or
Ph + > 0

• Check compliance
• Drug - drug interactions
• Mutational analysis

• Change to alternative TKI (if mutation (+), according to mutation profile)
• Same dose or increase current dose (for nilotinib and dasatinib)
• Evaluation of HSCT depending on response to 2nd line TKIs

Warning: $BCR-ABL1 0.1-1\%$

• Keep or increase current dose
• Change to alternative TKI (if mutation (+), according to mutation profile)
• More frequent RQ-PCR monitoring (even monthly)
**Any Time after 12 Months**

**Optimal:**

\[ BCR-ABL1 \leq 0.1\% \]

Continue current dose of TKI

Monitor RQ-PCR Q3-6M

**Failure:**

- Loss of CHR
- Loss of CCyR
- Confirmed loss of MMR
- Mutations
- CCA/Ph +

- Check compliance
- Drug - drug interactions
- Mutational analysis

**Warning:**

CCA/Ph- (-7 or 7q-)

- Change to alternative TKI (if mutation (+), according to mutation profile)
- Same dose or increase current dose (for nilotinib and dasatinib)
- Evaluation of HSCT depending on response to 2\textsuperscript{nd} line TKIs

- Keep or increase current dose
- Change to alternative TKI (if mutation (+), according to mutation profile)
- More frequent RQ-PCR monitoring (even monthly)
### Treatment Options Based on BCR-ABL1 Mutation Status

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>T315I</td>
<td>Ponatinib (clinical trial), HSCT</td>
</tr>
<tr>
<td>V299L</td>
<td>Nilotinib</td>
</tr>
<tr>
<td>T315A</td>
<td>Nilotinib, Imatinib</td>
</tr>
<tr>
<td>F317L/V/I/C</td>
<td>Nilotinib</td>
</tr>
<tr>
<td>Y253H, E255K/V,</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>F359V/C/I</td>
<td></td>
</tr>
<tr>
<td>Any other mutation</td>
<td>High-dose Imatinib, Dasatinib, Nilotinib</td>
</tr>
</tbody>
</table>

Excluding Bosutinib and Omacetaxine (currently not available in Taiwan)
Hematopoietic Stem Cell Transplantation (HSCT) Candidates

• Allo-SCT recommended in the following conditions:
  1) CP-- only for patients resistant to >= 2 TKIs or with T315I mutation.
  2) Disease progresses to AP or BP.
  3) BP at presentation: induction chemotherapy +/- TKI, then proceed to SCT, using myeloablative conditioning if possible.
  4) AP at presentation should search for donor and consider SCT unless optimal response with TKI achieved.

• For CP patients who fail to achieve CCyR, or lose CCyR, or lose confirmed MMR, but still in CHR and CP, HLA typing and allo-SCT may be considered if fully-matched donor available.

• For CP patients undergoing HSCT, either myeloablative or reduced-intensity conditioning may be used according to transplant center experience.
Following HSCT

HSCT

No CCyR, or in relapse

Frequent monitoring, withdrawal of immunosuppressants

CCyR(+) 

RQ-PCR monitoring q3M x 2 yrs, then q6M

Positive

In patients with prior AP or BP, consider TKI therapy post-HSCT for at least one year

Discuss options with transplant team:
- TKI
- DLI
- IFN
- Clinical trial

Negative*

Value of maintenance therapy with TKI after SCT is not proven, but seems intuitively logical.

*Relapse: confirmed loss of MMR

NCCN v1.2014 CML (Biol Blood Marrow Transplant. 2010, 16:639)
Following HSCT

• For patients transplanted at advanced phase, it is important to achieve full donor chimerism and deep molecular response within 1-3 months to prevent relapse
  – frequent monitoring by cytogenetic and molecular assays
  – tapering of immunosuppressants +/- DLI usually required for patients without CCyR, with mixed chimerism, or in relapse
• For patients with CCyR after HSCT, molecular monitoring should be checked every 3 months for 2 years then very 6 months until relapse.
• Very low level of BCR-ABL1 may be detected after SCT and its clinical significance is unclear. Monitor MRD level closely and only confirmed loss of MMR (IS > 0.1%) is regarded as relapse.
• Value of maintenance therapy with TKI after SCT is not proven, but seems intuitively logical.
  – in patients with prior AP or BP, consider TKI therapy post HSCT for at least one year
  – do not use imatinib post-HSCT in patients who have previously failed imatinib
Definition of Molecular Relapse Following Hematopoietic Stem Cell Transplantation

• $BCR-ABL / ABL > 0.02\%$ IS on 3 occasions
• $BCR-ABL / ABL > 0.05\%$ IS on 2 occasions
• Confirmed loss of MMR

Overview of Side Effects

• Major side effects (grade 3/4)

Typically occur during the first phase of treatment, are manageable, but require temporary treatment discontinuation and dose reduction, and can lead to treatment discontinuation in about 10% of patients.

• Minor side effects (grade 1/2)

Begin early during treatment and can become chronic and persist forever. They are manageable and tolerable, but affect the quality of life, and are a cause of decreased compliance, that is a major cause of failure.

• Late complications, so-called “off-target”, that can affect the CV system, heart and blood vessels, the respiratory system, liver, pancreas, the immune defense, second malignancies, calcium, glucose and lipid metabolism, etc.

* All TKIs can be toxic to the heart and should be used with great caution in patients with heart failure.
Recommendations for Dose Modification in CML-CP Patients Treated with Imatinib with Cytopenia

CML-CP with imatinib 400mg QD

↓

ANC < 1.0 x10⁹/L and/or PLT < 50 x10⁹/L (grade 3-4)

↓

Interrupt imatinib until ANC ≥ 1.0 x 10⁹/L and PLT ≥ 50 x 10⁹/L (≤ grade 2)

↓

Resume with imatinib 400mg QD

↓

Recurrence of ANC < 1.0 x10⁹/L and/or PLT < 50 x10⁹/L (grade 3-4)

↓

Interrupt imatinib until ANC ≥ 1.0 x 10⁹/L and platelets ≥ 50 x 10⁹/L (≤ grade 2)

↓

Resume with imatinib 300mg QD
Recommendations for Dose Modification in Advanced CML Patients Treated with Imatinib with Cytopenia

CML (AP/BC) with imatinib 600mg QD (or 400mg BID)

ANC < 0.5 x10^9/L and PLT < 10 x10^9/L (grade 4)

BM study (aspiration/biopsy) to confirm disease status

Cytopenia unrelated to disease (hypocellular BM)

Reduce dose: imatinib 400mg QD

If cytopenia persists for 2 weeks, reduce dose further to 300mg QD.
If cytopenia persists for 4 weeks, stop imatinib until ANC ≥ 1.0 x 10^9/L and PLT ≥ 20 x 10^9/L and resume 300mg QD.

Hypercellular BM with Blasts ≥ 20%

Continue 600mg or switch to dasatinib +C/T and/or HSCT
Recommendations on The Management of Non-Hematologic Toxicity of Imatinib

Very infrequently require permanent discontinuation and check for concomitant medications

- Hepatotoxicity – stop, restart and monitor carefully (check liver function test monthly)
  - ALT/AST > 5 X ULN or bilirubin > 3 X ULN (grade ≥ 3) : hold imatinib until ALT/AST < 2.5 X ULN and bilirubin < 1.5 X ULN grade ≤ 1), resume at starting dose or reduced dose
  - If recurrence of hepatotoxicity, consider switch to 2nd generation TKIs
- In patients with moderate renal impairment
  - GFR 20-39 mL/min: start 50% dose and increase dose as tolerated but ≤ 400mg/d.
  - GFR 40-59 mL/min: ≤ 600mg/d
- Fluid retention (pleural effusion, pericardial effusion, ascites and edema) – intermittent diuretics, dose interruption, dose reduction, or switch to 2nd generation TKIs (depend on severity)
- Muscle cramping: calcium supplement
- Nausea – take with meals and large glass of water
- Diarrhea – antispasmodics, check for lactase deficiency
- Rash – symptomatic medication (topical or systemic steroids), dose interruption, dose reduction, or switch to 2nd generation TKIs
Drug Interactions (Imatinib)*

- Imatinib metabolized by CYP3A4/5 (cytochrome P 450)
- Inducers will **reduce** plasma levels of imatinib
  - Anticonvulsants (phenobarbital, phenytoin, carbamazepine)
  - Dexamethasone
  - St. John’s wort (43% increase in clearance)
  - Rifampicin
- Inhibitors will **increase** plasma levels of imatinib
  - Cimetidine / ranitidine
  - Erythromycin / clarithromycin
  - Ketoconazole / itraconazole
  - Grapefruit juice
- Imatinib may increase plasma levels of
  - Cyclosporine A
  - HMG-CoA reductase inhibitors (simvastatin)
  - Warfarin (use heparin or LMW heparin)

*Blood 2011;117:e75-87*
Imatinib and Pregnancy

Recommendations

• Avoid imatinib during pregnancy
• Accidental or desired pregnancy
  Risk ↔ benefit evaluation
  Fetal abnormalities 10%
    100 x of normal population
• International pregnancy registry
## Managing a Planned Pregnancy

| Pre-conception                                                                 | • At least 24 months MR$^{4.5}$
| • Counseling                                                                  | • Rule-out common causes of male and female infertility |
| • Imatinib wash-out before trying to conceive                                 | • 7-10 days seems appropriate |
| Disease monitoring                                                            | • Monthly RQ-PCR |
| • No treatment if >MMR                                                       | • IFN if molecular relapse (?) |
| • Restart imatinib > 4 months of gestation                                    | • Breast feeding contraindicated |
| After delivery                                                                | 44 |
Special Considerations of 2nd Generation TKIs (Nilotinib/Dasatinib)

• All TKIs can be toxic to the heart and should be used with great caution in patients with heart failure.

• **Nilotinib** has been reported to be associated particularly with arterial pathology, peripheral and coronary.

• **Dasatinib** has been reported to be associated particularly with pleura and lung complications.

• **Nilotinib contraindication**: Past history of pancreatitis

• **Dasatinib contraindication**: Uncontrolled hypertension, COPD, CHF, chest wall injury, asthma, pneumonia, GI bleeding, auto-immune disorders, aspirin
Special Considerations of 2\textsuperscript{nd} Generation TKIs (Nilotinib/Dasatinib)

- Both drugs cause QTc prolongation
  (Avoid use of concomitant drugs known to prolong QT interval
  http://crediblemeds.org and strong CYP3A4 inhibitors)

1. Periodically monitoring of K\textsuperscript{+} and Mg\textsuperscript{++}, correct deficiencies prior to administration

2. ECGs (for QTc evaluation) should be obtained at baseline, 7 days after initiation and any dose adjustments
  - If QTc > 480 mSec: hold drug, correct hypokalemia or hypomagnesemia
  - If QTc < 450 mSec and within 20mSec of baseline within 2 weeks: resume therapy at prior dose
  - If QTc falls between 450~480 mSec after 2 wks: resume at one reduced level (400mg/d)
  - Following dose reduction if QTc returns to > 480 mSec, Nilotinib should be discontinued and ECG should be obtained 7 days after any subsequent dose adjustment to monitor QTc.
Recently Identified SAE in 2\textsuperscript{nd} TKIs

- Nilotinib
  - Peripheral arterial occlusive disease (PAOD)

- Dasatinib
  - Pulmonary arterial hypertension (PAH)
Drug Interactions (Nilotinib)*

- Nilotinib metabolized by CYP3A4
- CYP3A4 Inducers will **reduce** plasma levels of Nilotinib
  - Anticonvulsants (phenobarbital, phenytoin, carbamazepine)
  - Dexamethasone
  - St. John’s wort
  - Rifampin / rifabutin
- CYP3A4 Inhibitors will **increase** plasma levels of nilotinib
  - Ketoconazole / itraconazole / voriconazole
  - Clarithromycin
  - Atazanavir / indinavir / nelfinavir / ritonavir / saquinavir
- Nilotinib may increase plasma levels of
  - Pgp, CYP2C8, CYP2C9, CYP2D6 and CYP2C9
- Grapefruit juice should be avoided
- Avoid food 2 hours before and 1 hour after taking dose

*Blood 2011;117:e75-87*
Recommendations for Dose Modification in CML-CP Patients Treated with Nilotinib with Cytopenia

CML-CP with nilotinib 300mg BID

- ANC < 1.0 x 10^9/L and/or PLT < 50 x 10^9/L (grade 3-4)

  - Interrupt nilotinib until ANC > 1.0 x 10^9/L and PLT > 50 x 10^9/L

  - If recover < 2 weeks: Resume with nilotinib 300mg BID
  - If recover > 2 weeks: Resume with nilotinib 400mg QD
Recommendations on The Management of Non-Hematologic Toxicity of Nilotinib

**Liver toxicity:** (check liver function test monthly)

- Elevated serum levels of hepatic transaminases, bilirubin, lipase, and/or amylase (grade ≥ 3): hold drug until serum levels return to grade ≤ 1 and resume Nilotinib at 400mg QD

**Other non-hematologic toxicity**

- Grade 3-4: hold drug until grade 1 or better, then resume at 400mg QD

**Rare but serious toxicities**

- PAOD (peripheral arterial occlusive disease)
  - Evaluate patients for pre-existing PAOD and for vascular risk factors prior to initiating nilotinib and during treatment
  - If PAOD is confirmed, nilotinib should be permanently discontinued
Clinical Considerations Before Nilotinib

• Although infrequent, PAOD should be taken into account before initiating nilotinib with screening for vascular risk factors or pre-existing PAOD

• Risk factors for PAOD (similar to those for atherosclerosis)
  ➢ smoking, diabetes mellitus, dyslipidemia, hypertension, male gender, age > 50 years and obesity

• Ankle-brachial index (ABI) testing in individuals aged > 65
  ➢ normal : 1.00–1.40
  ➢ abnormal < 0.90
  ➢ borderline: 0.91–0.99

• Duplex ultrasonography to identify the involved arteries
Severe Peripheral Arterial Disease During Nilotinib Therapy

• Symptoms/signs
  ➢ intermittent claudication, usually in the calf

• Incidence (?)-variable
  ➢ Frontline nilotinib therapy: (retrospective analysis)
    ENESTnd trial: 7/556 (1.3% vs. 02% for imatinib) (Leukemia 2013)
    MDACC: 1/117 (0.85%)
  ➢ Second-line nilotinib therapy: (retrospective analysis)
    MDACC: 4 of 116 (3.44%)
    Other reports: 6.0~12.5% (Am J H 2011)

• Time of onset
  ➢ Variable: 4 ~ 72 months (median around 2-3 years)

• Therapeutic options
  ➢ angioplasty, stent, amputation
  ➢ Shift to another TKIs
Drug Interactions (Dasatinib)*

- Dasatinib metabolized by CYP3A4
- CYP3A4 Inducers will reduce plasma levels of Dasatinib
  - Anticonvulsants (phenobarbital, phenytoin, carbamazepine)
  - Dexamethasone
  - St. John’s wort (hypericum perforatum)
  - Rifampicin
- CYP3A4 Inhibitors will increase plasma levels of Dasatinib
  - Ketoconazole / itraconazole
  - Erythromycin / clarithromycin
  - Ritonavir / atazanavir / indinavir / nelfinavir / saquinavir
- Dasatinib may increase plasma levels of
  - Alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus
  - Ergot alkaloids (ergotamine, dihydroergotamine)
- Grapefruit juice should be avoided
- Antacids (if needed, took at least 2 hours prior or after Dasatinib)
- H2 Blockers / Proton pump inhibitors (famotidine, omeprazole)

*Blood 2011;117:e75-87
Recommendations for Dose Modification in CML-CP Patients Treated with Dasatinib with Cytopenia

CML-CP with dasatinib 100mg QD

ANC < 0.5-1.0 x10⁹/L (grade 3-4) or PLT < 25 x10⁹/L (grade 4)

Interrupt dasatinib until ANC ≥ 1.0 x 10⁹/L and PLT ≥ 50 x 10⁹/L

If recover ≤ 7days

Resume with dasatinib 100mg QD

Resume with dasatinib 70mg QD (second episode)

Resume with dasatinib 50mg QD (for newly diagnosed patients) or discontinue dasatinib if third episode

If ANC < 0.5 x10⁹/L or PLT < 25 x10⁹/L > 7 days
Recommendations for Dose Modification in Advanced CML Patients Treated with Dasatinib with Cytopenia

CML (AP/BP) with dasatinib 140mg QD

- ANC < 0.5 x10⁹/L and PLT < 10 x10⁹/L (grade 4)

BM study (aspiration/biopsy) to confirm disease status

- Cytopenia unrelated to disease (hypocellular BM), Interrupt dasatinib until ANC ≥ 1.0 x 10⁹/L and PLT ≥ 20 x 10⁹/L
  - Resume dasatinib 140mg QD
  - If cytopenia recurs, repeat above step and resume therapy at 100mg QD (second episode) or 70mg QD (third episode).

- Hypercellular BM with Blasts ≥ 20%
  - Consider escalating dose to 180mg QD or change treatment
Recommendations on The Management of Non-Hematologic Toxicity of Dasatinib

If a severe, non-hematologic, adverse reaction (≥ Grade 3) develops, treatment must be hold until the event resolved or improved. Treatment can be resumed at starting dose or reduced dose depending on the severity of AE.

**Specific interventions**

- Fluid retention events (pleural effusion, pericardial effusion, ascites and edema): diuretics, supportive care.
- Pleural/Pericardial effusion: diuretics and dose interruption; short course of steroids (prednisolone 20mg/D x 3) if significant symptoms
- When resolved: reduce one dose level
- GI upset – take with meals and large glass of water
- Rash – symptomatic medication (topical or systemic steroids), dose interruption, dose reduction, or switch to 2nd generation TKIs

**Rare but serious toxicities**

- Pulmonary Arterial Hypertension (PAH): may occur anytime during treatment
  - Screen by echocardiography prior to and during treatment; right heart catheterization to confirm Pulmonary Hypertension
  - If PAH is confirmed, dasatinib should be permanently discontinued
  - May be reversible on discontinuation of dasatinib but not completely
Pulmonary Arterial Hypertension in Patients Treated with Dasatinib

- Symptoms/signs
  - Cough, dyspnea, peripheral edema, pleural effusion, hepatosplenomegaly, RV failure
- Incidence (\(?)\)
  - 13/2900 (0.45\%) in French PH registry, compared with none in 8750 imatinib- and 900 nilotinib-treated patients (Circulation 2012)
- Time of onset
  - 2 to 3 years after dasatinib treatment
- Most completely recovered within 4-6 months after withdrawal of dasatinib
- Further treatment option
  - Shift to another TKIs
Management Protocol for Pleural Effusion Emerging on Dasatinib therapy

1. **Evidence of pleural effusion** (cough, dyspnea, chest pain, etc)

2. **Chest X-ray to confirm diagnosis**

3. **Determine severity of confirmed event**

   - **Upon resolution, resume therapy at a reduced dose**:
     - Chronic phase: 70 mg QD or 100 mg 5 days/week with a weekend drug holiday;
     - Accelerated phase or blast crisis: 40–50 mg twice daily

   - **If adverse event does not improve within 7 days**, diuretics and steroids may be used as supportive care

   - **Severe adverse events** may require thoracentesis and oxygen therapy

4. **Interrupt dasatinib therapy**
   - Use steroids 50 mg/day for 2 days followed by 30 mg/day for 5 days

5. **Severe adverse events** may require thoracentesis and oxygen therapy

   - **BMS 2009**
   - **NCCN 2010**