CML Diagnosis and Management
Lymphoma Tumor Board
September 15, 2017
Mechanisms of BCR-ABL activity in CML and blast crisis

BCR-ABL

Stimulation of signaling and proliferation and decreased apoptosis leading to expansion of the myeloid compartment

CP-CML

BCR-ABL via ROS

H$_2$O$_2$

- OH

Progression to BC

DNA damage and impairment of DNA repair leading to genetic instability and clonal evolution with ACA in up to 80% of cases and multiple mutations within and outside the BCR-ABL kinase domain

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BCR/ABL influences DNA mutation in multiple ways
BCR-ABL Imatinib-Resistance Mutations

- Height of the bars indicates frequency of mutation
- P-loop: M237I, G244V, D241G
NCCN Guidelines Version 1.2018
Chronic Myeloid Leukemia

WORKUP

- H&P, including spleen size by palpation (cm below costal margin)
- CBC with differential
- Chemistry profile
- Bone marrowa aspirate and biopsy for morphologic and cytogenetic evaluation
- Quantitative RT-PCR (QPCR) using International Scale (IS) for BCR-ABL1 (blood)
- Hepatitis panel (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [HBsAb], hepatitis B core antibody [anti-HBc], IgM anti-HBc, IgG anti-HBc)

CLINICAL PRESENTATION

Ph positive or BCR-ABL1 positive

Chronic phase CML

Ph negative and BCR-ABL1 negative

Advanced phase CML

Evaluate for diseases other than CML

Determine risk score (See Risk Calculation Table CML-A)

Additional testing
- Flow cytometry to determine cell lineage
- Mutational analysis
- HLA testing, if considering allogeneic HCT (See CML-6)

Accelerated phaseb

Blast phaseb

See Primary Treatment (CML-2)

See Primary Treatment (CML-4)

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
CLINICAL PRESENTATION

Chronic phase CML

Treatment Considerations:
- Patient comorbidities and drug toxicities
- Monitor response
- Evaluate patient compliance and drug interactions
- Early toxicity monitoring

Low-risk score (See Risk Calculation Table CML-A)

First generation TKI (Imatinib or generic imatinib 400 mg QD) (category 1)
or Second generation TKI (Dasatinib 100 mg QD [category 1]) orNilotinib 300 mg BID [category 1]) orClinical trial

Intermediate- or high-risk score (See Risk Calculation Table CML-A)

First generation TKI (Imatinib or generic imatinib 400 mg QD) orSecond generation TKI (Dasatinib 100 mg QD) orNilotinib 300 mg BID orClinical trial

See Response Milestones and Treatment Options (CML-3)³

See Response Milestones and Treatment Options (CML-3)³

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³See Monitoring Response to TKI Therapy and Mutational Analysis (CML-C).
⁴Long-term follow-up data suggest that patients with an intermediate- or high-risk Sokal or Hasford score may preferentially benefit from dasatinib or nilotinib. See Discussion for additional information.
# NCCN Guidelines Version 1.2018
Chronic Myeloid Leukemia

## RESPONSE MILESTONES
c\(^e\)

<table>
<thead>
<tr>
<th>BCR-ABL1 (IS)</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>&gt;12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10%(^f)</td>
<td>YELLOW</td>
<td></td>
<td>RED</td>
<td></td>
</tr>
<tr>
<td>&gt;1%-10%</td>
<td></td>
<td>GREEN</td>
<td>YELLOW</td>
<td>RED</td>
</tr>
<tr>
<td>0.1%-1%</td>
<td></td>
<td></td>
<td></td>
<td>GREEN</td>
</tr>
<tr>
<td>&lt;0.1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CLINICAL CONSIDERATIONS**

- RED = Evaluate patient compliance and drug interactions
- YELLOW = Evaluate patient compliance and drug interactions
- GREEN = Monitor response (CML-F) and side effects

**SECOND-LINE AND SUBSEQUENT TREATMENT OPTIONS**

- RED = Switch to alternate TKI (CML-5) and Evaluate for HCT (CML-6)
- YELLOW = Switch to alternate TKI (CML-5) or Continue same TKI (CML-F)
- GREEN = Continue same TKI (CML-F)

\(^f\) See Monitoring Response to TKI Therapy and Mutational Analysis (CML-C).
\(^e\) See Criteria for Hematologic, Cytogenetic, and Molecular Response and Relapse (CML-D).
\(^g\) Achievement of response milestones must be interpreted within the clinical context. Patients with more than 50% reduction compared to baseline or minimally above the 10% cutoff can continue the same dose of dasatinib or nilotinib for another 3 months.

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CLINICAL PRESENTATION

Treatment Considerations
- Evaluate for allogeneic HCT
- Disease progression to advanced phase while on TKI therapy has worse prognosis than presenting with advanced phase CML.
- Treatment options are based on patient comorbidities and age.
- Selection of TKI is based on prior therapy and/or BCR-ABL mutation profile.
- CNS involvement has been described in blast phase CML. Lumbar puncture and CNS prophylaxis is recommended for lymphoid blast phase.

Advanced phase CML → Accelerated phase

Clinical trial or TKI (CML-F) or Omacetaxine (CML-F)

Lymphoid → Blast phase

Clinical trial or ALL-type induction chemotherapy + TKI (CML-F) (See NCCN Guidelines for Acute Lymphoblastic Leukemia)
or TKI (CML-F) + steroids

Myeloid

Clinical trial or AML-type induction chemotherapy + TKI (CML-F) (See NCCN Guidelines for Acute Myeloid Leukemia)
or TKI (CML-F)

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See Definitions of Accelerated Phase and Blast Phase (CML-B).
Omacetaxine is a treatment option for patients with disease progression to accelerated phase CML. Omacetaxine is not a treatment option for patients who present with accelerated phase CML.
## TREATMENT OPTIONS BASED ON BCR-ABL1 MUTATION PROFILE

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Treatment Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y253H, E255K/V, or F359V/C/I</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>F317L/V/I/C, T315A, or V299L</td>
<td>Nilotinib</td>
</tr>
<tr>
<td>E255K/V, F317L/V/I/C, F359V/C/I, T315A, or Y253H</td>
<td>Bosutinib</td>
</tr>
<tr>
<td>T315I</td>
<td>Ponatinib, ^k Omacetaxine, ^l allogeneic HCT (CML-6), or clinical trial</td>
</tr>
</tbody>
</table>

^k^ Ponatinib is a treatment option for patients with a T315I mutation or for patients for whom no other TKI is indicated.

^l^ Omacetaxine is a treatment option for patients with disease that is resistant and/or intolerant to 2 or more TKIs.

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#### Chronic Myeloid Leukemia

**RISK CALCULATION TABLE**

<table>
<thead>
<tr>
<th>Study</th>
<th>Calculation</th>
<th>Risk Definition by Calculation</th>
</tr>
</thead>
</table>
| Sokal et al, 1984¹     | $\text{Exp(0.0116 \times (age in years - 43.4) + (spleen - 7.51) + 0.188 \times ((platelet count + 700)^2 - 0.563) + 0.0887 \times (blast cells - 2.10))}$ | Low: $<0.8$
|                        |                                                                                                                         | Intermediate: $0.8$ - $1.2$
|                        |                                                                                                                         | High: $>1.2$ |
| Hasford et al, 1998²   | $0.666 \text{ when age } \geq 50 \text{ years } + (0.042 \times \text{spleen}) + 1.0956 \text{ when platelet count } > 1500 \times 10^9/L + (0.0584 \times \text{blast cells}) + 0.20399 \text{ when basophils } > 3\% + (0.0413 \times \text{eosinophils}) \times 100$ | Low: $\leq780$
|                        |                                                                                                                         | Intermediate: $781$ - $1480$
|                        |                                                                                                                         | High: $>1480$ |

Calculation of relative risk found at [http://www.icsg.unibo.it/rrcalc.asp](http://www.icsg.unibo.it/rrcalc.asp). Age is in years. Spleen is in centimeter below the costal margin (maximum distance). Blast cells, eosinophils, and basophils are in percents of peripheral blood differential. All factors must be collected prior to any treatment.


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Chronic Myeloid Leukemia

DEFINITION OF ACCELERATED PHASE\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Modified Criteria Used at MD Anderson Cancer Center\textsuperscript{3,4} (most commonly used in clinical trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Peripheral blood blasts $\geq 15%$ and $&lt;30%$</td>
</tr>
<tr>
<td>• Peripheral blood blasts and promyelocytes combined $\geq 30%$</td>
</tr>
<tr>
<td>• Peripheral blood basophils $\geq 20%$</td>
</tr>
<tr>
<td>• Platelet count $\leq 100 \times 10^9$/L unrelated to therapy</td>
</tr>
<tr>
<td>• Additional clonal cytogenetic abnormalities in Ph+ cells</td>
</tr>
</tbody>
</table>

DEFINITIONS OF BLAST PHASE\textsuperscript{1}

<table>
<thead>
<tr>
<th>World Health Organization (WHO) Criteria\textsuperscript{5}</th>
<th>International Bone Marrow Transplant Registry\textsuperscript{6}</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Blasts $\geq 20%$ of peripheral white blood cells or of nucleated bone marrow cells</td>
<td>• $\geq 30%$ blasts in the blood, marrow, or both</td>
</tr>
<tr>
<td>• Extramedullary blast proliferation</td>
<td>• Extramedullary infiltrates of leukemic cells</td>
</tr>
<tr>
<td>• Large foci or clusters of blasts in the bone marrow biopsy</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{1}The table refers to myeloblasts. Any increase in lymphoblasts is concerning for (nascent) blast phase.


\textsuperscript{5}From Jaffe ES, Harris NL, Stein H, et al. WHO Classification of Tumours, Pathology, and Genetics of Tumours of Haematopoietic and Lymphoid Tissues, IARC, Lyon, 2001.


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<table>
<thead>
<tr>
<th>Test</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow cytogenetics&lt;sup&gt;1&lt;/sup&gt;</td>
<td>• At diagnosis</td>
</tr>
<tr>
<td></td>
<td>• Failure to reach response milestones</td>
</tr>
<tr>
<td></td>
<td>• Any sign of loss of response (defined as hematologic or cytogenetic relapse)</td>
</tr>
<tr>
<td>Quantitative RT-PCR (QPCR) using IS</td>
<td>• At diagnosis</td>
</tr>
<tr>
<td></td>
<td>• Every 3 months after initiating treatment. After <em>BCR-ABL1</em> 0.1%–1% (IS) has</td>
</tr>
<tr>
<td></td>
<td>been achieved, every 3 months for 2 years and every 3–6 months thereafter</td>
</tr>
<tr>
<td></td>
<td>• If there is 1-log increase in <em>BCR-ABL1</em> transcript levels with MMR, QPCR</td>
</tr>
<tr>
<td></td>
<td>should be repeated in 1–3 months</td>
</tr>
<tr>
<td>BCR-ABL kinase domain mutation analysis</td>
<td>• Chronic phase</td>
</tr>
<tr>
<td></td>
<td>• Failure to reach response milestones</td>
</tr>
<tr>
<td></td>
<td>• Any sign of loss of response (defined as hematologic or cytogenetic relapse)</td>
</tr>
<tr>
<td></td>
<td>• 1-log increase in <em>BCR-ABL1</em> transcript levels and loss of MMR</td>
</tr>
<tr>
<td></td>
<td>• Disease progression to accelerated or blast phase</td>
</tr>
</tbody>
</table>

<sup>1</sup>FISH has been inadequately studied for monitoring response to treatment.
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Chronic Myeloid Leukemia

CRITERIA FOR HEMATOLOGIC, CYTOGENETIC, AND MOLECULAR RESPONSE AND RELAPSE

Complete hematologic response\(^1\)
- Complete normalization of peripheral blood counts with leukocyte count <10 x 10\(^9\)L
- Platelet count <450 x 10\(^9\)L
- No immature cells, such as myelocytes, promyelocytes, or blasts in peripheral blood
- No signs and symptoms of disease with disappearance of palpable splenomegaly

Cytogenetic response\(^2,3\)
- Complete cytogenetic response (CCyR) - No Ph-positive metaphases\(^4\)
- Partial cytogenetic response (PCyR) - 1%-35% Ph-positive metaphases
- Major cytogenetic response - 0%-35% Ph-positive metaphases\(^5\)
- Minor cytogenetic response - >35% Ph-positive metaphases

Molecular response\(^5,6\)
- Early molecular response (EMR) - BCR-ABL1 ≤10% (IS) at 3 and 6 months
- Major molecular response (MMR) - BCR-ABL1 <0.1% (IS) or ≥3-log reduction in BCR-ABL1 mRNA from the standardized baseline, if QPCR (IS) is not available
- Complete molecular response (CMR) - no detectable BCR-ABL1 mRNA using a QPCR assay with a sensitivity of at least 4.5 logs below the standardized baseline. CMR is variably described, and is best defined by the the assay's level of sensitivity (eg, MR 4.5).

Relapse
- Any sign of loss of response (defined as hematologic or cytogenetic relapse)
- 1-log increase in BCR-ABL1 transcript levels with loss of MMR should prompt bone marrow evaluation for loss of CCyR but is not itself defined as relapse (eg, hematologic or cytogenetic relapse)

\(^2\)A minimum of 20 metaphases should be examined.
\(^4\)CCyR typically correlates with BCR-ABL1(IS) 0.1%-1%.

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