National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Chronic Myelogenous Leukemia

Version 2.2011

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NCCN Guidelines™ Version 2.2011 Panel Members
Chronic Myelogenous Leukemia

NCCN Guidelines Index
CML Table of Contents
Discussion

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NCCN Guidelines Panel Disclosures

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NCCN Guidelines™ Version 2.2011 Table of Contents
Chronic Myelogenous Leukemia

NCCN Guidelines Index
CML Table of Contents
Discussion

NCCN Chronic Myelogenous Leukemia Panel Members

Summary of Guidelines Updates (Updates)
Workup (CML-1)
Primary Treatment (CML-1)
3-Month Follow-up Therapy (CML-2)
6-Month Follow-up Therapy (CML-3)
12-Month Follow-up Therapy (CMl-4)
18-Month Follow-up Therapy (CML-5)
Disease Progression (CML-6)
Hematopoietic stem cell transplantation (CML-7)
Monitoring For Patients Receiving Tyrosine Kinase Inhibitor Therapy (CML-A)
Supportive Care Strategies for Leukocytosis and Thrombocytosis (CML-B)
Management of Imatinib Toxicity (CML-C)
Management of Nilotinib Toxicity (CML-D)
Important Considerations with Nilotinib (CML-E)
Management of Dasatinib Toxicity (CML-F)
Criteria for Cytogenetic, Hematologic and Molecular Response (CML-G)
Management of Interferon Toxicity (CML-H)
Definitions of Accelerated Phase (CML-I)
Definitions of Blast Crisis (CML-J)

Clinical Trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

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NCCN Guidelines™ Version 2.2011 Updates Chronic Myelogenous Leukemia

NCCN Guidelines Index
CML Table of Contents
Discussion

The Discussion section was updated in the 2.2011 version of the Chronic Myelogenous Leukemia guidelines, see MS-1.

Summary of the changes in the 1.2011 version of the Chronic Myelogenous Leukemia guidelines from the 2.2010 version include:

CML-1
- H&P - "including spleen size by palpation (cm below costal margin)" was added.
- Discussion of treatment options - "imatinib" changed to "tyrosine kinase inhibitor."
- Nilotinib 300 mg BID or Dasatinib 100 mg daily added as treatment options for the primary treatment of Ph1 positive or BCR-ABL positive CML. Both recommendations have a category 1 designation.
- Footnote "d" - updated to reflect 8 years of follow-up data are available.
- Footnote "h" - updated reference.
- Footnote "j" - allogeneic HSCT added as an option for patients that are unable to tolerate TKI therapy.

CML-2
- "Complete" added to "hematologic remission."
- "Not in hematologic remission, or in hematologic relapse" changed to "Less than complete hematologic response."
- Complete hematologic response - nilotinib or dasatinib were added to continue as treatment, if used as primary therapy.
- Footnote "o" is new to the page: "Same dose of TKI should be continued indefinitely and not be discontinued."
- Footnote "p" is new to the page - "There are some data regarding the efficacy of second generation TKIs against specific mutations." Also applies to CML-3 through CML-5.
- Footnote "q" is new to the page - "Patients with failure to a first-line TKI, should be treated with an alternate TKI in the second-line setting." Also applies to CML-3 through CML-7.

CML-3
- Complete cytogenetic response or partial response; Minor cytogenetic response - nilotinib or dasatinib were added to continue as treatment, if used as primary therapy.

CML-4
- Complete cytogenetic response; Partial cytogenetic response - nilotinib or dasatinib were added to continue as treatment, if used as primary therapy.
- Cytogenetic relapse - "Evaluate patient compliance and drug-drug interactions" and "Consider mutational analysis" added.

CML-5
- Complete cytogenetic response - nilotinib or dasatinib were added to continue as treatment, if used as primary therapy.
- The category for "Minor or no cytogenetic response" was removed.
- Partial cytogenetic response - "Evaluate patient compliance and drug-drug interactions and Consider mutational analysis" added.
- Partial cytogenetic response; cytogenetic relapse - "increase dose of imatinib" removed as a treatment option.

CML-6
- This page lists recommendations for disease progression on first-line therapy (changed from disease progression on imatinib).
- Workup added to "accelerated phase."
- Mutational analysis added to the workup for accelerated phase and blast crisis.
- Accelerated phase - wording for HSCT changed to "Consider HSCT based on response."
- Blast crisis (lymphoid) - "ALL-type induction chemotherapy + dasatinib followed by HSCT" - dasatinib changed to TKI.
- Blast crisis (myeloid) - "AML-type induction chemotherapy + dasatinib followed by HSCT" - dasatinib changed to TKI.
- Footnote "v" is new to the page - "Selection of TKI (imatinib, dasatinib, nilotinib) is based on prior therapy and/or mutational testing."

CML-7
- "Complete" added to "cytogenetic remission."

CML-A
- Listed indications for mutational analysis - "may provide additional information" changed to "is recommended."

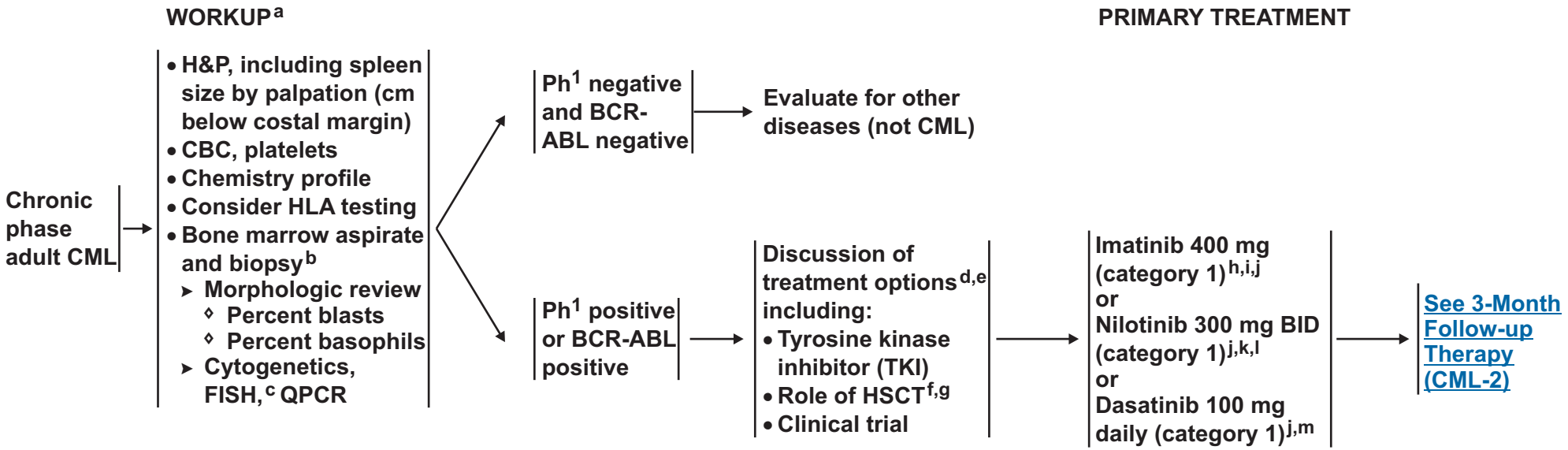
CML-C
- Non-hematologic toxicity recommendations - Grade 3, change to Grade 2-3. Updates made according to package insert. Also applies to CML-D and CML-F.

CML-D
- Updates made according to package insert. Dose levels added.

CML-F
- Updates made according to package insert. Dose reduction changed from 80 mg daily to 70-80 mg.

NCCN Guidelines™ Version 2.2011
Chronic Myelogenous Leukemia

NCCN Guidelines Index
CML Table of Contents
Discussion



[a] See Monitoring for Patients Receiving Tyrosine Kinase Inhibitor therapy (CML-A).

[b] Bone marrow is preferable for the initial workup, not only to provide morphologic review, but also to detect chromosomal abnormalities that are not detectable on peripheral blood FISH.

[c] See text for further discussion regarding the role of FISH in the initial workup of patients with CML.

[d] There is 8 year follow-up data which shows clear evidence of excellent survival benefit with imatinib. See text for additional information.

[e] For patients with symptomatic leukocytosis or thrombocytosis, see Supportive Care Strategies (CML-B).

[f] HSCT = hematopoietic stem cell transplantation. Refers to a matched related or unrelated allogeneic transplant. HLA testing should be performed if considering HSCT.

[g] Indications and outcomes of related and unrelated transplant are age, donor type and transplant center dependent. Nonmyeloablative transplant is under investigation and should be performed only in the context of a clinical trial.

[h] There are data suggesting a faster time to MMR with a higher dose of imatinib but whether this is an important endpoint in long term outcome is unknown. Cortes JE, Baccarani M, Guilhot F, et al. Phase III, randomized, open-label study of daily imatinib mesylate 400 mg versus 800 mg in patients with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase using molecular end points: tyrosine kinase inhibitor optimization and selectivity study. J Clin Oncol 2010;28:424-430.

[i] See Management of Imatinib Toxicity (CML-C).

[j] Rare patients unable to tolerate imatinib, dasatinib, or nilotinib then consider IFN/PEG-IFN, allogeneic HSCT or clinical trial.

[k] See Management of Nilotinib Toxicity (CML-D).

[l] See Important Considerations with Nilotinib (CML-E).

[m] See Management of Dasatinib Toxicity (CML-F).

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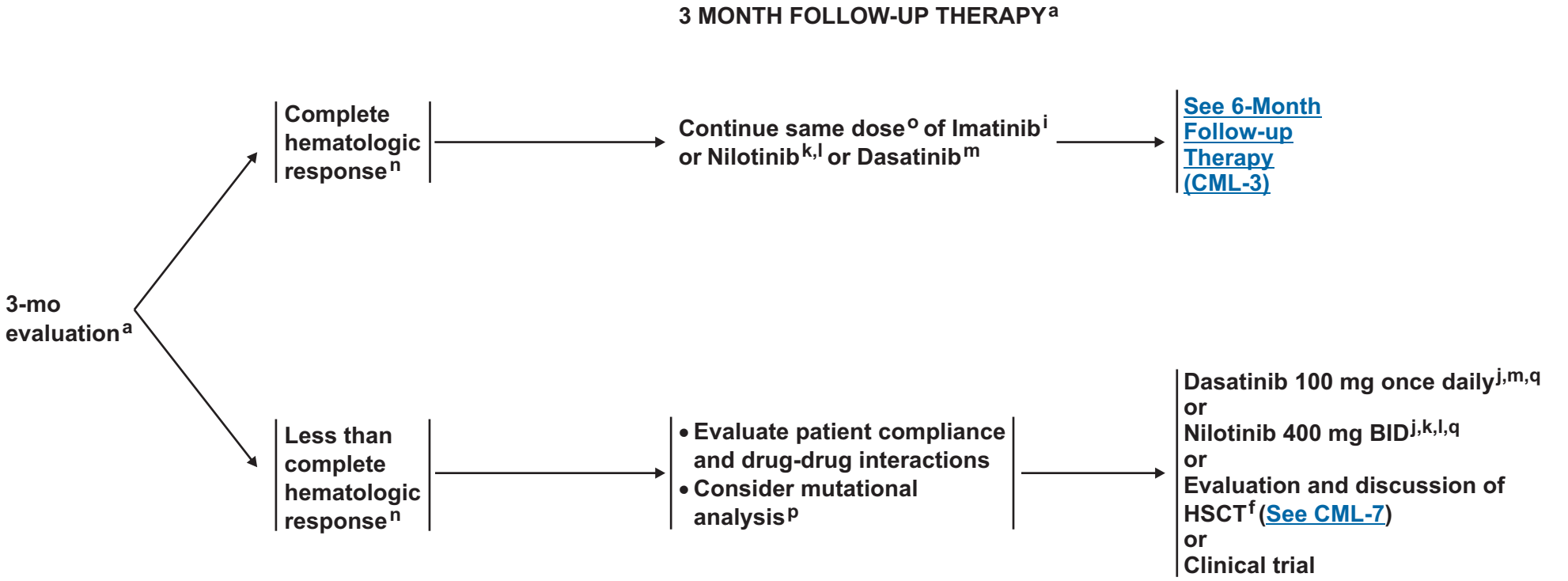

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[n] See Criteria for Cytogenetic, Hematologic and Molecular Response (CML-G).
[o] Same dose of TKI should be continued indefinitely and not be discontinued.
[p] There are some data regarding the efficacy of second generation TKIs against specific mutations.
[q] Patients with failure to a first-line TKI, should be treated with an alternate TKI in the second-line setting.

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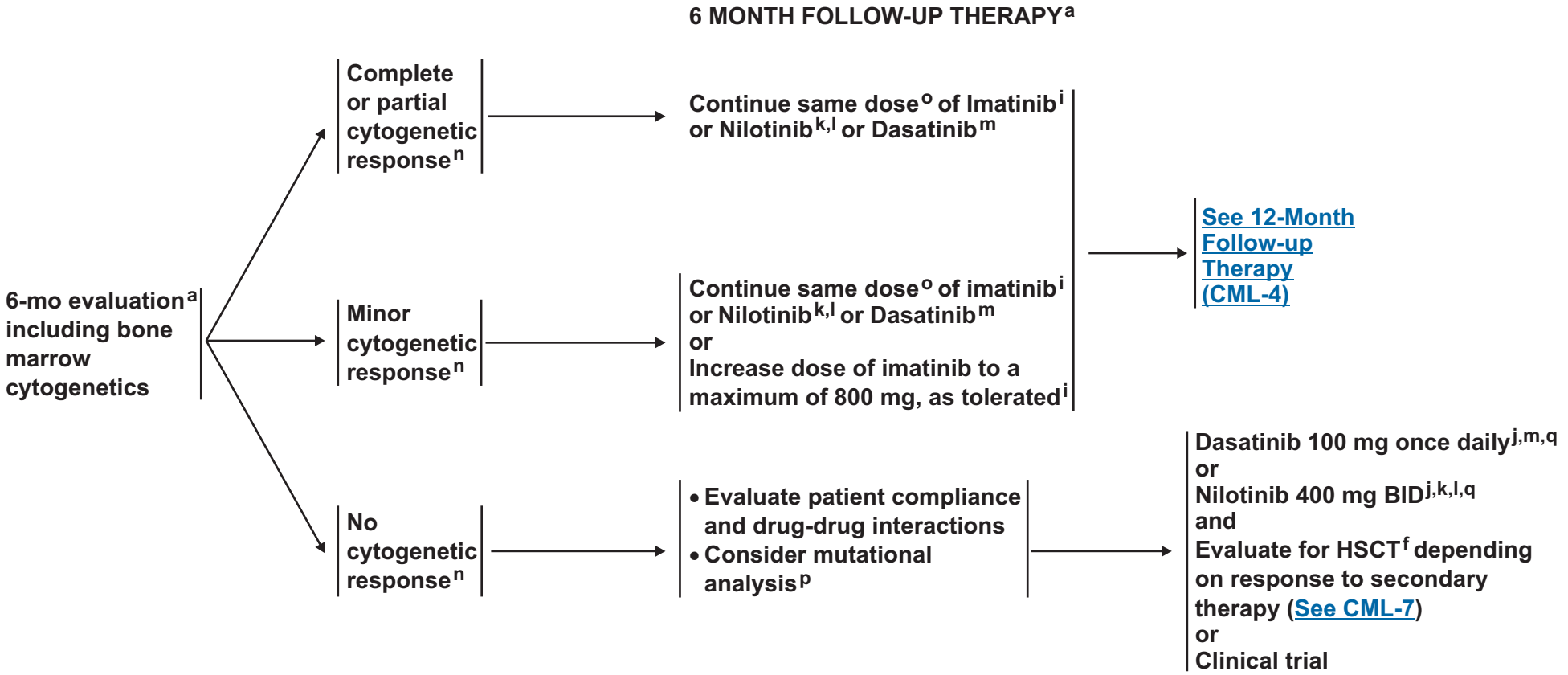

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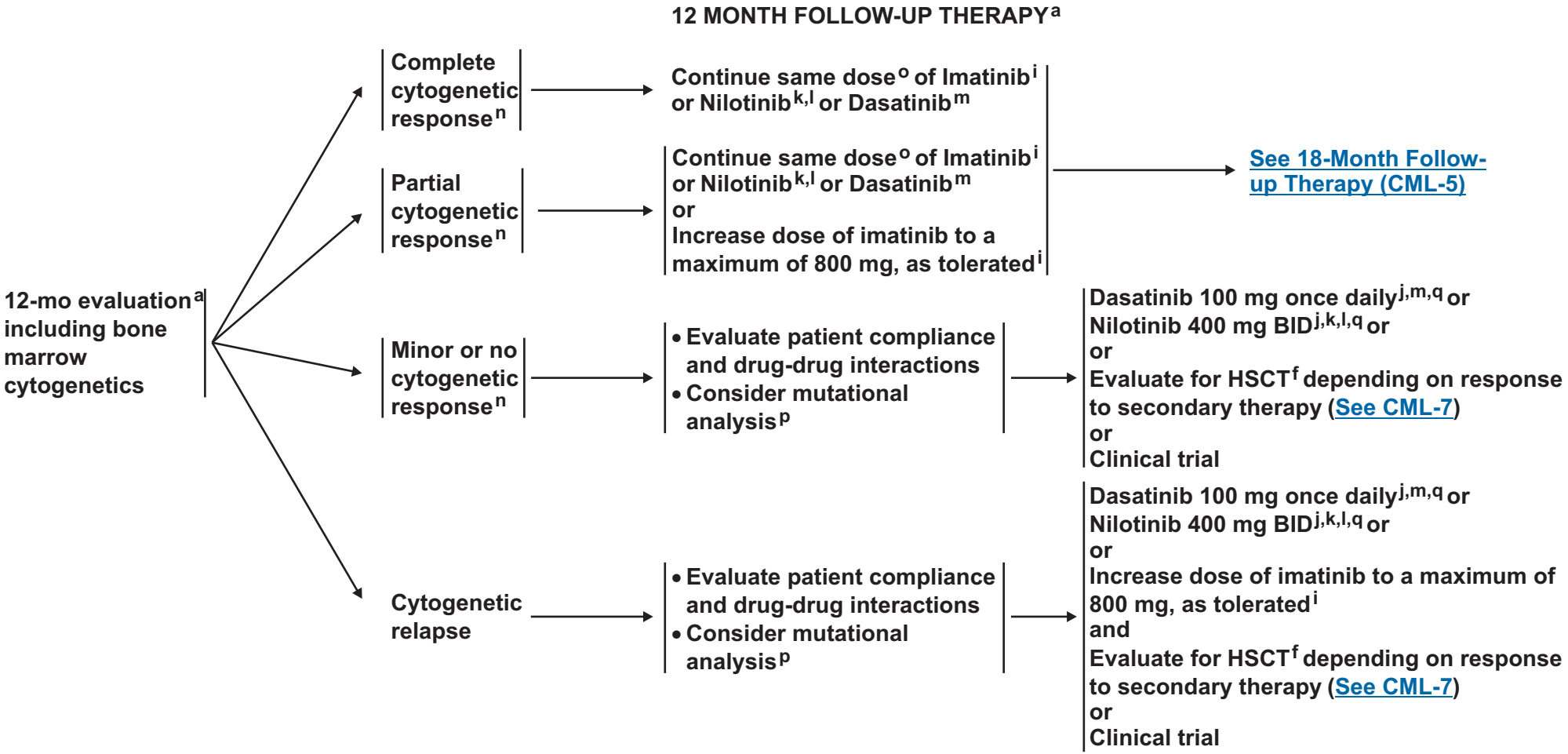

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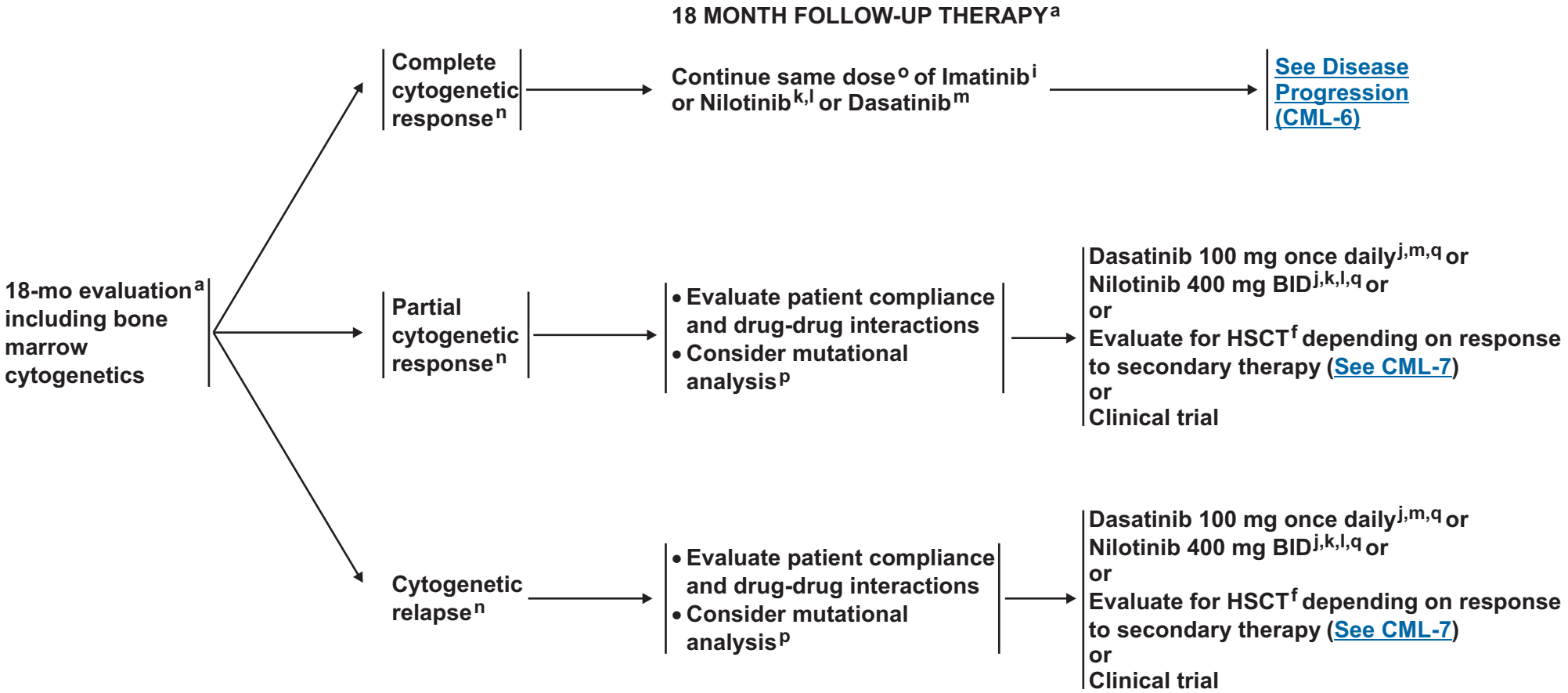

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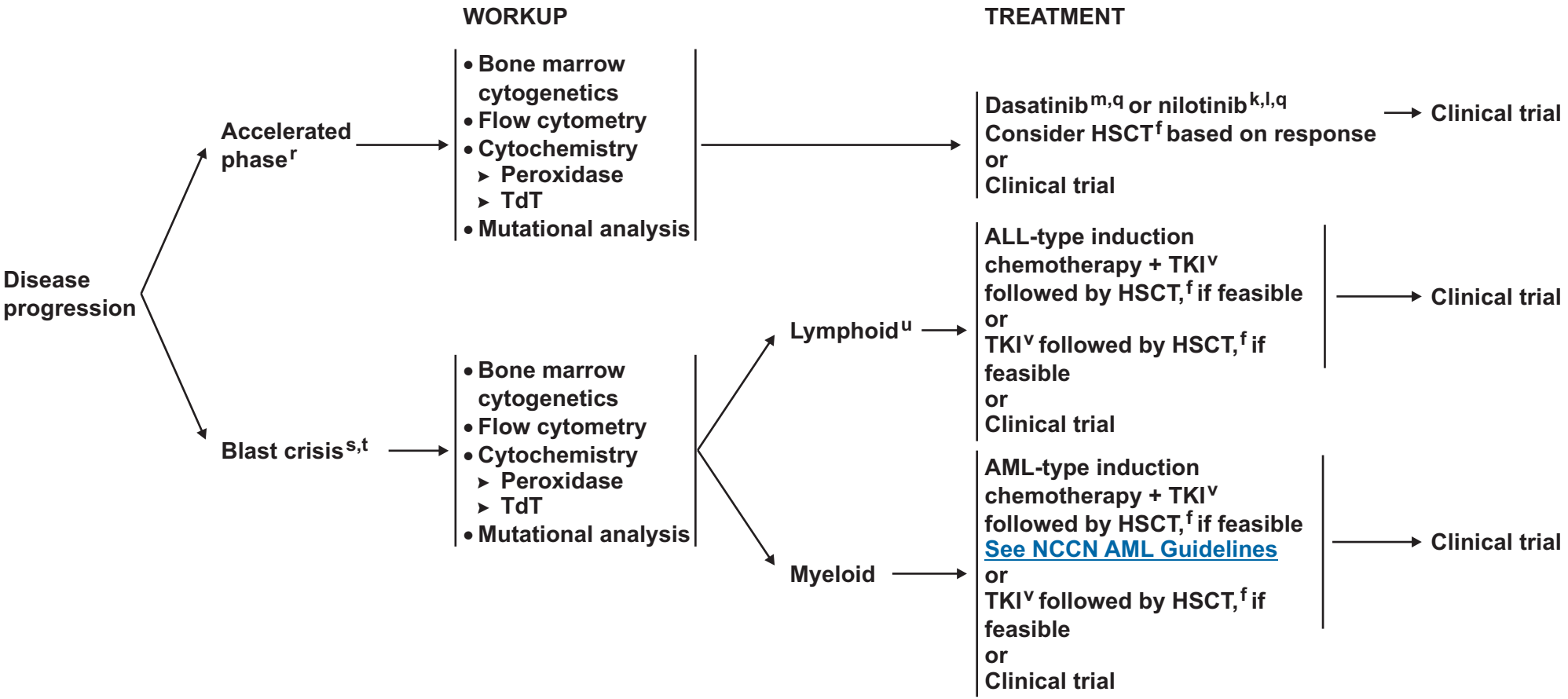

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[q] Patients with failure to a first-line TKI, should be treated with an alternate TKI in the second-line setting.

[r] See Definitions of Accelerated Phase (CML-I).

[s] See Definitions of Blast Crisis (CML-J).

[t] Patients presenting with de novo Ph+ acute leukemia or de novo accelerated or blast phase should be considered for combination chemotherapy + TKI (imatinib or dasatinib) or clinical trial.

[u] Consider CNS prophylaxis/treatment.

[v] Selection of TKI (imatinib, dasatinib, nilotinib) is based on prior therapy and/or mutational testing.

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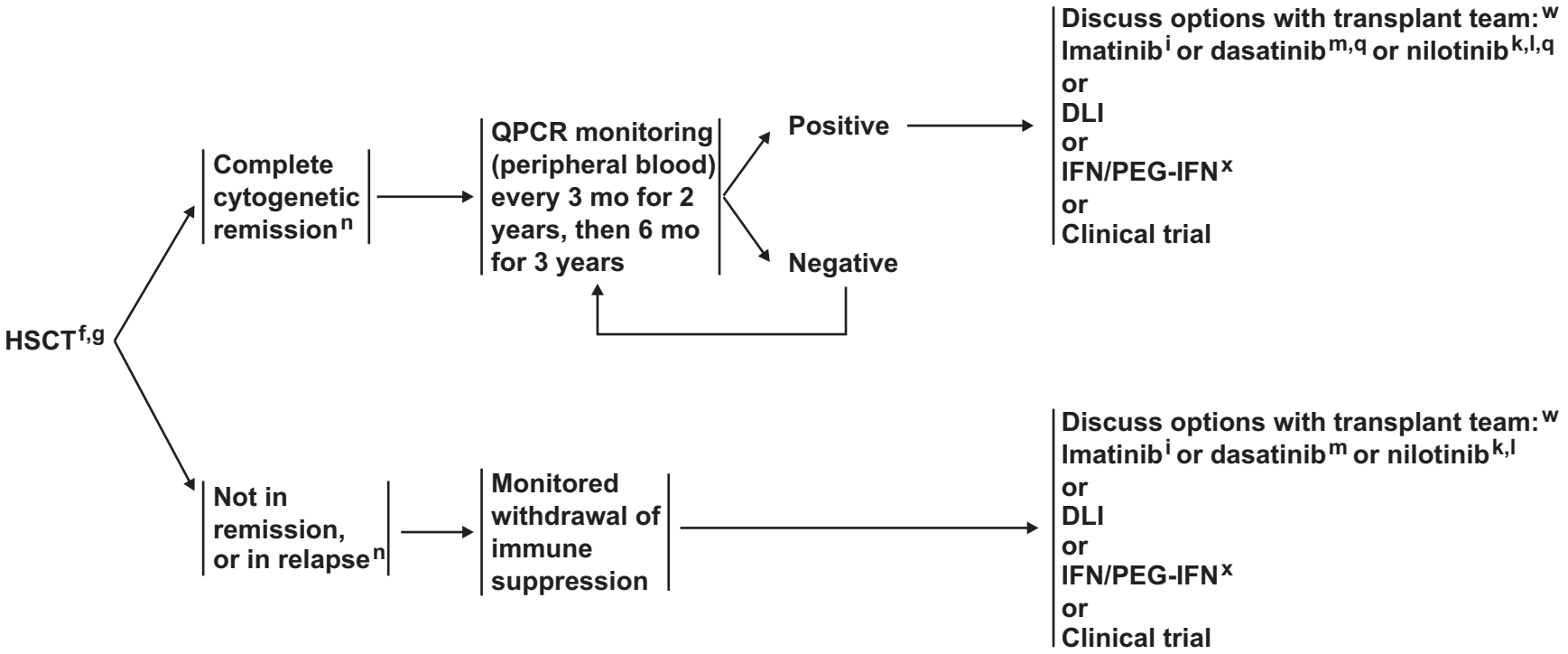
FOLLOW-UP THERAPY



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[l] See Important Considerations with Nilotinib (CML-E).

[m] See Management of Dasatinib Toxicity (CML-F).

[n] See Criteria for Cytogenetic, Hematologic and Molecular Response (CML-G).

[q] Patients with failure to a first-line TKI, should be treated with an alternate TKI in the second-line setting.

[w] There are data for imatinib posttransplant but not in patients who have previously failed imatinib. Other TKIs may be more appropriate although there are no published data to support their use posttransplant.

[x] See Management of IFN Toxicity (CML-H).

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MONITORING FOR PATIENTS RECEIVING TYROSINE KINASE INHIBITOR THERAPY[1]

Indications for cytogenetics and QPCR for BCR-ABL mRNA

- **Diagnosis of CML**
  - **Bone marrow cytogenetics and measurement of BCR-ABL transcript numbers by QPCR before initiation of treatment.**
  - **If collection of BM is not feasible, fluorescence in situ hybridization (FISH) on a PB specimen using dual probes for the BCR and ABL genes is an acceptable method of confirming the diagnosis of CML.**
- **Treatment Response**
  - **BCR-ABL transcript levels should be measured every 3 months.**
  - **Bone marrow cytogenetics at 6 and 12 months from initiation of therapy. If complete cytogenetic response (CCyR) at 6 mo, it is not necessary to repeat bone marrow cytogenetics at 12 mo.**
  - **Bone marrow cytogenetics at 18 months if patient not in a CCyR at 12 months.**
- **Complete Cytogenetic Response**
  - **BCR-ABL transcript levels should be measured every 3-6 months.**
  - **Bone marrow cytogenetics as clinically indicated.**
- **Rising level (1 log increase) of BCR-ABL transcripts**
  - **Evaluate patient compliance**
  - **Rising levels (1 log increase) with major molecular response (MMR) repeat in 1-3 mo.**
  - **Rising levels (1 log increase) without MMR, obtain bone marrow cytogenetics.**
  - **Mutation testing should be considered (see below).**

ABL kinase domain (KD) mutation analysis

- **Chronic phase CML**
  - **ABL KD mutation screening is recommended if there is inadequate initial response (failure to achieve complete hematologic response at 3 months, minimal cytogenetic response at 6 months or major cytogenetic response at 12 months) or any sign of loss of response (defined as hematologic relapse, cytogenetic relapse or 1 log increase in BCR-ABL transcript ratio and loss of MMR).**
- **Progression to accelerated or blast phase CML**
  - **Testing for KD mutations is recommended.**

[1]Hughes T, Deininger M, Hochhaus A, et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood 2006;108(1):28-37.

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SUPPORTIVE CARE STRATEGIES FOR LEUKOCYTOSIS AND THROMBOCYTOSIS

Factors to consider when choosing treatment include: patient's age, risk factors for thromboembolic disease, and degree of thrombocytosis.

Symptomatic leukocytosis:

- **Treatment options include hydroxyurea, apheresis, imatinib or clinical trial**

Symptomatic thrombocytosis:

- **Treatment options include hydroxyurea, antiaggregants, anagrelide or apheresis**

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MANAGEMENT OF IMATINIB TOXICITY[1,2]

Hematologic

- **Grade 3-4 neutropenia [absolute neutrophil count [ANC] < 1000/mm^3]: Hold drug until ANC ≥ 1500/mm^3, then resume imatinib at the starting dose of 400 mg. If recurrence of ANC < 1000/mm^3, hold drug until ANC ≥ 1500/mm^3, then resume imatinib at reduced dose of 300 mg.**
- **Grade 3-4 thrombocytopenia (platelet count < 50,000/mm^3): Hold drug until platelet count ≥ 75,000/mm^3, then resume imatinib at the starting dose of 400 mg. If recurrence of platelet count < 50,000/mm^3, hold drug until platelet count ≥ 75,000/mm^3, then resume imatinib at reduced dose of 300 mg.**
- **Accelerated phase and blast phase: Patients may have cytopenias related to disease. If cytopenia is unrelated to disease, reduce dose to 400 mg. If cytopenia persists 2 weeks, reduce dose further to 300 mg. If cytopenia persists for 4 weeks, stop imatinib until ANC ≥ 1000/mm^3 and platelet count ≥ 20,000/mm^3, and then resume treatment at 300 mg.**
- **Growth factors can be used in combination with imatinib for patients with resistant neutropenia.[3]**
- **Grade 3-4 anemia[4]**

Specific Interventions

- **Diarrhea: supportive care**
- **Edema: diuretics, supportive care**
- **Fluid retention (pleural effusion, pericardial effusion, edema, and ascites): diuretics, supportive care, dose reduction, interruption or discontinuation. Consider echocardiogram to check LVEF.**
- **GI upset: take medication with a meal and large glass of water**
- **Muscle cramps: calcium supplement, tonic water**
- **Rash: topical or systemic steroids, dose reduction, interruption or discontinuation**

Nonhematologic

- **Grade 2-3: Use specific interventions, listed above. If not responsive to symptomatic measures, treat as Grade 4.**
- **Grade 4: Hold drug until grade 1 or better, then consider resuming dose at 25-33% dose reduction (not less than 300 mg). Consider change to dasatinib, nilotinib or clinical trial.**

Nonhematologic - Liver

- **Grade 2, hold drug until grade ≤ 1. Resume at 25-33% dose reduction (not less than 300 mg). Evaluate for other hepatotoxic drugs that may be contributing to toxicity, including acetaminophen. Consider change to dasatinib, nilotinib or clinical trial.**
- **Grade 3-4: Consider change to dasatinib, nilotinib or clinical trial.**

[1] Please refer to package insert for full prescribing information, available at www.fda.gov.
[2] Many toxicities are self-limiting, consider re-escalating dose at a later time.
[3] Quintas-Cardama A, Kantarjian H, O'Brien S, et al. Granulocyte-colony-stimulating factor (filgrastim) may overcome imatinib-induced neutropenia in patients with chronic-phase chronic myelogenous leukemia. Cancer 2004;100(12):2592-2597.
[4] Although erythropoietin is effective, guidelines from the Centers for Medicaid and Medicare Services (CMS) and the Food and Drug Administration (FDA) do not support the use of Erythropoietic Stimulating Agents (ESAs) in myeloid malignancies.

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MANAGEMENT OF NILOTINIB TOXICITY[1]

QT Interval Prolongation

- **ECGs with a QTc > 480 msec: Hold drug. If serum potassium and magnesium levels are below lower limit of normal, correct with supplements to within normal limits. Resume within 2 weeks at prior dose if QTcF is less than 450 msec and within 20 msec of baseline. If QTcF is between 450 and 480 msec after 2 weeks, resume at reduced dose (400 mg once daily). Following dose reduction, if QTcF returns to > 480 msec, nilotinib should be discontinued. ECG should be obtained 7 days after any dose adjustment to monitor QTc.**

Hematologic

- **Grade 3-4 neutropenia (absolute neutrophil count [ANC] < 1000/mm^3):Hold drug until ANC is ≥ 1000/mm^3, resume at prior dose if recovery occurs within 2 weeks, or reduce the dose to 400 mg once daily, if ANC is < 1000/mm^3 for more than 2 weeks.**
- **Grade 3-4 thrombocytopenia (platelet count < 50,000/mm^3): Hold drug until the platelet count is ≥ 50,000/mm^3, resume at prior dose if recovery occurs within 2 weeks or reduce the dose to 400 mg once daily, if platelet count is < 50,000/mm^3 for more than 2 weeks.**
- **Growth factors can be used in combination with nilotinib for patients with resistant neutropenia and thrombocytopenia.**
- **Grade 3-4 anemia[2]**

Specific Interventions

- **Headache: Supportive care**
- **Nausea: Supportive care**
- **Diarrhea: Supportive care**
- **Rash: Topical or systemic steroids, dose reduction, interruption or discontinuation**

Nonhematologic

- **Grade 2-3: Use specific interventions, listed above.**
  If not responsive to symptomatic measures, treat as Grade 4
- **Grade 4: Hold drug until grade 1 or better, and then resume at reduced dose level (400 mg once daily).**
  If clinically appropriate, consider escalating dose to 300-400 mg twice daily, depending on starting dose.

Nonhematologic - Liver

- **Elevated serum levels of lipase, amylase, bilirubin and/or hepatic transaminases (grade ≥ 3):**
  Hold drug until serum levels return to grade ≤ 1. Resume nilotinib at 400 mg once daily.

Dose Levels (chronic phase - first-line setting)		
0	300 mg	twice daily
-1	400 mg	once daily

Dose Levels (chronic phase - second-line setting, accelerated or blast phase)		
0	400 mg	twice daily
-1	400 mg	once daily

[1] Please refer to package insert for full prescribing information, available at www.fda.gov.

[2] Although erythropoietin is effective, recent guidelines from the Centers for Medicaid and Medicare Services (CMS) and the Food and Drug Administration (FDA) do not support the use of Erythropoietic Stimulating Agents (ESAs) in myeloid malignancies.

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IMPORTANT CONSIDERATIONS WITH NILOTINIB[1]

- **Nilotinib prolongs the QT interval. Sudden deaths have been reported in patients receiving nilotinib.**
- **Nilotinib should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected prior to nilotinib administration and should be periodically monitored.**
- **Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided.**
- **Patients should avoid food 2 hours before and 1 hour after taking dose.**
- **A dose reduction is recommended in patients with hepatic impairment.**
- **ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.**

[1]Please refer to package insert for full prescribing information, available at www.fda.gov.

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MANAGEMENT OF DASATINIB TOXICITY[1]

Hematologic

- Grade 4 neutropenia (absolute neutrophil count [ANC] < 500/mm^3): Hold drug until ANC ≥ 1000/mm^3, resume at original starting dose if recovery occurs within 7 days or reduce one dose level if ANC < 500/mm^3 for more than 7 days.
- Grade 3-4 thrombocytopenia (platelet count < 50,000/mm^3): Hold drug until platelet count ≥ 50,000/mm^3, resume at original starting dose if recovery occurs within 7 days or reduce one dose level if platelet count < 25,000/mm^3 for more than 7 days.
- Accelerated phase and blast phase: Patients may have cytopenias related to disease. If cytopenia is unrelated to disease, hold drug until ANC ≥ 1000/mm^3 and platelet count ≥ 20,000/mm^3, resume at original starting dose or reduce one dose level if cytopenia persists. If cytopenia is related to leukemia, consider dose escalation to 180 daily.
- Growth factors can be used in combination with dasatinib for patients with resistant neutropenia and thrombocytopenia.
- Grade 3-4 anemia[2]

Specific Interventions

- Fluid retention events (ascites, edema, pleural and pericardial effusion) are managed with diuretics, supportive care
- Pleural/pericardial effusion: diuretics, dose interruption. If pt has significant symptoms, consider short course of steroids (prednisone 20 mg/day x 3); when resolved, reduce one dose level.
- Headache: Supportive care
- GI upset: take medication with a meal and large glass of water
- Diarrhea: supportive care
- Rash: topical or systemic steroids, dose reduction, interruption or discontinuation

Nonhematologic

- Grade 2-3:
  - Use specific interventions, listed above
  - If not responsive to symptomatic measures, treat as Grade 4
- Grade 4:
  - Hold drug until grade 1 or better, and then consider resuming at reduced dose level depending on the severity of the initial event or change to nilotinib or imatinib.

Dose Levels (chronic phase)		
0	100 mg	once daily
-1	70-80 mg	once daily

Dose Levels (accelerated or blast phase)		
0	140 mg	once daily
-1	100 mg	once daily
-2	70-80 mg	once daily

[1] Please refer to package insert for full prescribing information, available at www.fda.gov.

[2] Although erythropoietin is effective, recent guidelines from the Centers for Medicaid and Medicare Services (CMS) and the Food and Drug Administration (FDA) do not support the use of Erythropoietic Stimulating Agents (ESAs) in myeloid malignancies.

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

CRITERIA FOR CYTOGENETIC, HEMATOLOGIC AND MOLECULAR RESPONSE[1]

Complete hematologic response
- 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

Partial hematologic response

Same as complete hematologic response, except for:
- Presence of immature cells
- Platelet count < 50% of the pretreatment count, but > 450 x 10^9/L
- Persistent splenomegaly, but < 50% of the pretreatment extent

Cytogenetic response[2]
- Complete- No Ph[1]-positive metaphases
- Partial- 1%-35% Ph-positive metaphases
- Major- 0%-35% Ph-positive metaphases (complete + partial)
- Minor- >35% Ph-positive metaphases

Molecular response
- Complete molecular response - BCR-ABL mRNA undetectable by RT-PCR
- Major molecular response ≥ 3-log reduction of BCR-ABL mRNA

[1]Adapted, with permission, from Faderl S et al: Chronic myelogenous leukemia: Biology and therapy. Ann Intern Med 1999;131:207-219. The American College of Physicians-American Society of Internal Medicine is not responsible for the accuracy of the translation.
[2]A minimum of 20 metaphases should be examined.

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MANAGEMENT OF INTERFERON TOXICITY

Management:

- Depression: antidepressants (eg, fluoxetine, paroxetine)
- Thyroid function: monitor every 6 mo if marked fatigue
- Pulmonary function tests if respiratory distress

Dose modification:

- CNS toxicity
  - Memory changes
  - Concentration problems
  - Fatigue grade 2-3

Discontinue IFN if patient has:

- Suicidal tendencies
- Parkinsonism
- Autoimmune hemolytic anemia
- Pulmonary, cardiac toxicity (rare)
- Any grade 3 toxicity not responsive to dose reduction

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

DEFINITIONS OF ACCELERATED PHASE

Criteria of Sokal et al[1]

- Peripheral blood or marrow blasts ≥ 5%
- Basophils > 20%
- Platelet count ≥ 1000 x 10^9/L despite adequate therapy
- Clonal evolution
- Frequent Pelger-Huet-like neutrophils, nucleated erythrocytes, megakaryocyte nuclear fragments
- Marrow collagen fibrosis
- Anemia or thrombocytopenia unrelated to therapy
- Progressive splenomegaly
- Leukocyte doubling time < 5 days
- Fever of unknown origin

International Bone Marrow Transplant Registry Criteria[2]

- Leukocyte count difficult to control with hydroxyurea or busulfan
- Rapid leukocyte doubling time (< 5 days)
- Peripheral blood or marrow blasts ≥ 10%
- Peripheral blood or marrow blasts and promyelocytes ≥ 20%
- Peripheral blood basophils and eosinophils ≥ 20%
- Anemia or thrombocytopenia unresponsive to hydroxyurea or busulfan
- Persistent thrombocytosis
- Clonal evolution
- Progressive splenomegaly
- Development of myelofibrosis

Criteria Used at M.D. Anderson Cancer Center[3]

- Peripheral blood blasts ≥ 15%
- Peripheral blood blasts and promyelocytes ≥ 30%
- Peripheral blood basophils ≥ 20%
- Platelet count ≤ 100 x 10^9/L unrelated to therapy
- Clonal evolution

Adapted, with permission, from Faderl S, et al. Chronic myelogenous leukemia: Biology and therapy. Ann Intern Med 1999; 131:207-219. The American College of Physicians-American Society of Internal Medicine is not responsible for the accuracy of the translation.

World Health Organization (WHO) Criteria[4]

- Blasts 10-19% of WBCs in peripheral and/or nucleated bone marrow cells
- Peripheral blood basophils ≥ 20%
- Persistent thrombocytopenia (< 100 x 10^9/L) unrelated to therapy, or persistent thrombocytosis (> 1000 x 10^9/L) unresponsive to therapy
- Increasing spleen size and increasing WBC count unresponsive to therapy
- Cytogenetic evidence of clonal evolution

[1] Sokal JE, Baccarani M, Russo D, et al. Staging and prognosis in chronic myelogenous leukemia. Semin Hematol 1988;25(1):49-61.
[2] Savage DG, Szydlo RM, Chase A, et al. Bone marrow transplantation for chronic myeloid leukemia: The effects of differing criteria for defining chronic phase on probabilities of survival and relapse. Br J Haematol 1997;99:30-35.
[3] Kantarjian HM, Deisseroth A, Kurzrock R, et al. Chronic myelogenous leukemia: A concise update. Blood 1993;82:691-703.
[4] Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (Eds.): World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press: Lyon 2008.

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

DEFINITIONS OF BLAST CRISIS

World Health Organization (WHO) Criteria[1]	International Bone Marrow Transplant Registry[2]
• Blasts ≥ 20% of peripheral blood white cells or of nucleated bone marrow cells • Extramedullary blast proliferation • Large foci or clusters of blasts in the bone marrow biopsy	• ≥ 30% blasts in the blood, marrow, or both • Extramedullary infiltrates of leukemic cells

[1] Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (Eds.): World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press: Lyon 2008.

[2] Druker BJ. Chronic Myelogenous Leukemia In: DeVita VT, Lawrence TS, Rosenburg SA, eds. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. Vol. 2 (ed 8): Lippincott, Williams and Wilkins; 2007:2267-2304.©

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

Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Chronic myelogenous leukemia (CML) accounts for 15% of adult leukemias. The median age of disease onset is 67 years; however, CML occurs in all age groups (SEER statistics). In 2010, an estimated 4,870 cases will be diagnosed in the USA, and 440 patients will die from the disease.[1]

CML is a hematopoietic stem cell disease, which is characterized by a reciprocal translocation between chromosomes 9 and 22, resulting in the formation of the Philadelphia chromosome (Ph chromosome). This translocation t(9;22) results in the head-to-tail fusion of the breakpoint cluster region (BCR*)* gene on chromosome 22 at band q11 and the Abelson murine leukemia (ABL) gene located on chromosome 9 at band q34.[2] The product of the fusion gene (*BCR-ABL*) is believed to play a central role in the initial development of CML.

The *BCR-ABL* gene encodes a protein ($p210^{BCR\text{-}ABL}$), with deregulated tyrosine kinase activity. This protein contains NH_2-terminal domains of *BCR* and the COOH-terminal domains of *ABL*. Another fusion protein, p190, may be produced, but this is usually in the setting of Ph-positive acute lymphocytic leukemia (ALL). The oncogenic potential of the BCR-ABL fusion proteins has been validated by their ability to transform hematopoietic progenitor cells *in vitro* and *in vivo*.

The mechanisms by which $p210^{BCR\text{-}ABL}$ promote the transition from a benign state to a malignant state are not entirely understood. However, attachment of the *BCR* sequences to *ABL* results in three critical functional changes: (1) the ABL protein becomes constitutively active as a protein tyrosine kinase enzyme; (2) the DNA protein binding activity of ABL is attenuated; and (3) the binding of ABL to cytoskeletal actin microfilaments is enhanced. These effects increase proliferation, affect differentiation, and block apoptosis.

CML occurs in three difference phases (chronic, accelerated and blast phase) and is usually diagnosed in the chronic phase. However, gene expression profiling has shown a close correlation of gene expressions between the accelerated phase and blast crisis. The bulk of the genetic changes in progression occur in the transition from chronic phase to accelerated phase.[3] The activation of beta-catenin-signaling pathway in CML granulocyte-macrophage progenitors (which enhances the self-renewal activity and leukemic potential of these cells) may also be a key pathobiologic event in evolution to blast crisis CML.[4] Untreated chronic phase CML will eventually progress to advanced phase disease in 3-5 years.[5]

Sokal and Hansford are the two prognostic scoring systems available for the risk stratification of patients with CML. The Sokal score was developed in the chemotherapy era and it is based on patient's age, spleen size, platelet count and the percentage of blasts in the peripheral blood.[6] The Hasford model is applicable to patients treated with interferon. It includes eosinophils and basophils in the peripheral blood in addition to the same clinical variables used in the Sokal model.[7] The scoring systems stratify patients into three risk groups: low, intermediate and high (Table 1). The Sokal scoring system has been used to stratify the patients by risk in all the imatinib clinical trials.

NCCN CML guidelines discuss the clinical management of chronic phase, disease progression to accelerated or blast phase and monitoring response to treatment.

Tyrosine Kinase Inhibitor (TKI) Therapy for CML

Imatinib mesylate

Imatinib mesylate (formerly known as STI-571) is a selective inhibitor of the BCR-ABL tyrosine kinase.[8, 9] Initial trials with imatinib showed a marked effect as a second line therapy in patients in chronic phase who had failed interferon therapy or those with more advanced stage disease (accelerated phase or blast crisis).[10] At 5-year follow-up, complete cytogenetic response (CCyR) was seen in 41% of patients and 44% of patients remain on imatinib. Estimated rates of freedom from progression (FFP) to accelerated phase or blast phase and overall survival (OS) at 6-years were 61% and 76% respectively.[11]

Newly diagnosed patients were evaluated in the IRIS (International Randomized Study of Interferon and ST1571) trial. In this trial, 1106 patients were randomized to receive initial therapy with either 400 mg of daily imatinib or interferon-alpha plus low-dose cytarabine.[12] Crossover was allowed for treatment failure or intolerance. With a median follow-up of 19 months, the major cytogenetic response (MCyR) rate at 18 months was 87.1% in the imatinib group versus 34.7% in the control group. The estimated rate of CCyR was 76.2% with imatinib and 14.5% with interferon (P<.001). The estimated rate of freedom from progression to more advanced stage disease was 96.7% in the imatinib arm and 91.5% in the interferon-based arm (P<.001). In addition to its significantly greater efficacy, imatinib was also much better tolerated than the combination of interferon plus cytarabine.

In May 2001, the FDA (Food and Drug Administration) first approved imatinib mesylate for the advanced stages of CML. In December 2002, based on the results of IRIS study, FDA approved imatinib for the first-line treatment of patients with CML.

Long-term follow-up data of the IRIS trial are now available.[13,14] With a median follow-up of 60 months, estimated cumulative rates of CCyR among patients receiving imatinib were 69% at 12 months and 87% at 60 months. Only 7% of patients had progressed to accelerated-phase CML or blast crisis. OS was 89% at 60 months for patients who received imatinib as initial treatment.[13] Estimated 8-year event-free survival (EFS), FFP to accelerated or blast phase and OS were 81%, 92%, and 85% respectively.[14] Major molecular response (MMR) increased from 24% at 6 months and 39% at 12 months to the best observed MMR rate of 86% with 8-year follow-up. None of the patients with documented MMR at 12 mo progressed to accelerated phase blast crisis. These results demonstrate that continuous treatment of chronic phase CML with imatinib induces durable responses in large proportion of the patients with a decreasing rate of relapse. These data confirm the high durable response rates with imatinib in a large proportion of patients.

However, due to the high rate of crossover (90%) from interferon-alpha to imatinib mesylate within a year of study, survival benefit for imatinib mesylate versus interferon could not be demonstrated in the IRIS trial. In historical comparisons, survival benefit was significantly better for imatinib compared to interferon.[15, 16] Recently, Guilhot and colleagues reported the safety and efficacy of imatinib in 359 patients who crossed over from interferon-alpha plus cytarabine to imatinib in the IRIS study.[17] After a median follow-up of 54 months on imatinib, 93% achieved CHR; MCyR and CCyR were observed in 86% and 81% of patients respectively. Estimated rates of freedom from progression to accelerated or blast phase and overall survival were 91% and 89%, respectively, at 48 months after starting imatinib.

Imatinib mesylate is generally well tolerated. Frequently reported grade 3 or 4 toxicities include neutropenia and thrombocytopenia. Most frequently reported adverse events include gastrointestinal disturbances, edema, rash, and musculoskeletal complaints, but none of these led to discontinuation of treatment.[18] Hypophosphatemia, with associated changes in bone and mineral metabolism has been noted in a small group of patients.[19] Hematologic and non-hematologic toxicities caused by imatinib, as well as specific, panel-recommended interventions, are summarized in the algorithm. Erythropoietin and filgrastim has been shown to be effective in patients who develop imatinib-induced anemia and neutropenia, respectively.[20, 21] However, recent guidelines from the Centers for Medicare & Medicaid (CMS) and the FDA do not support the use of erythropoietic stimulating agents (ESAs) in myeloid malignancies. See “Management of Imatinib Toxicity” in the guidelines.

Cardiotoxicity

In a recent trial, long-term imatinib treatment was associated with congestive heart failure (CHF) and cardiotoxicity.[22] However, this appears to be very rare, as shown by the recent analysis of 1276 patients treated with imatinib at M.D. Anderson Cancer Center.[23] After a median follow-up of 47 months, 22 (1.7%) patients were found to have CHF during imatinib therapy. Out of these patients, 13 of them had received prior treatment with cardiotoxic drugs. The authors concluded that CHF is uncommon among patients receiving imatinib and its incidence rates are similar to those that occur in the general population. Patients with previous cardiac history should be monitored carefully. Aggressive medical therapy is recommended for symptomatic patients.

High-dose imatinib

Most patients retain variable levels of residual molecular disease at the 400 mg dose of imatinib. Several studies have evaluated the efficacy of high-dose imatinib in newly diagnosed patients.[24-26] Imatinib dosed at 600 or 800 mg daily was well tolerated and was also associated with superior cytogenetic and molecular response rates.[24, 25] In a phase II multicenter study [Rationale and Insight for Gleevec High-Dose Therapy (RIGHT)], newly diagnosed patients (n = 115; 70% Sokal low risk) treated with 400 mg imatinib twice daily achieved rapid and deep responses.[26] CHR at 6, 12, and 18 months was achieved and maintained in 93%, 94%, and 93% of evaluable patients, respectively. The rate of MCyR at 12 and 18 months was 90% and 96% respectively, and the corresponding CCyR rates were 85% and 83% respectively. MMR rates were 48% and 54% at 6 months and 12 months, respectively. The response rates were also higher in this trial compared to historic controls that received 400 mg daily in the IRIS trial. At 12 months, MMR was 54% for patients in the RIGHT trial compared with an estimated 39% for the historical control group. At 18 months, MCyR and CCyR rates were 90% and 85%, respectively, in the RIGHT trial compared with an estimated 85% and 69%, respectively, in the historical control group. The investigators of the TIDEL (The Australian Therapeutic Intensification in De Novo Leukemia) trial also reported

superior responses (MMR at 12 and 24 months were 55% and 77% respectively) in patients receiving 600 mg of imatinib as the initial dose compared to those receiving less than 600 mg (MMR at 12 and 24 months were 32% and 53% respectively).[24]

The efficacy of high dose (800 mg) imatinib as front-line therapy in intermediate and high Sokal risk patients with chronic phase CML has been evaluated by the GIMEMA CML working party and the European LeukemiaNet Study group respectively.[27, 28] The results of the phase II trial by the GIMEMA CML working party indicated that high dose imatinib is effective in inducing rapid cytogenetic and molecular responses in intermediate Sokal risk patients.[27] The response rates at 12 months were better than those documented in the IRIS study for intermediate risk patients treated with 400 mg imatinib. The European LeukemiaNet Study, which randomized high Sokal risk patients to receive 800 mg or 400 mg of imatinib, did not show a significant benefit for high dose imatinib.[28] The CCyR at one year was 64% and 58% for high and standard dose imatinib respectively. No differences were detectable in CCyR rates at 3 and 6 months or in the molecular response rates at any time.

TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity) study is an open-label phase III randomized trial comparing the efficacy of higher dose imatinib and standard dose imatinib in patients with newly diagnosed chronic phase CML.[29] This trial randomized 476 patients to receive either high dose imatinib (800 mg; 400 mg twice daily) or standard dose imatinib (400 mg once daily). High dose imatinib was well tolerated in most patients and was also associated with more rapid responses than the standard dose. However, MMR and CCyR at 12 months were comparable between arms (MMR: 46% vs. 40%, respectively; CCyR: 70% vs. 66% respectively). In patients with high Sokal risk scores, MMR rates at 12 months were 51% for high dose imatinib compared to 31% for standard. The MMR rate also correlated with average dose intensity. At 12 months, MMR was observed in 83 (62%) of 134 patients with an average dose intensity of 600 to 799 mg/d, and it was observed in 26 (38%) of 69 patients with an average dose intensity of 400 to 599 mg/d.

Additional studies and long-term follow-up from the ongoing trials are needed to determine whether high dose imatinib should be implemented as front-line therapy in a risk-adapted fashion.

Dasatinib

Dasatinib (formerly known as BMS-354825) is a potent, orally available ABL kinase inhibitor, similar to imatinib, but with the added advantage in that it can bind to both the active and inactive conformation of the ABL kinase domain. As a result, dasatinib is active against nearly all imatinib-resistant *BCR-ABL* mutations in vitro.[30]

In a phase I dose escalation study, dasatinib induced hematologic and cytogenetic responses in those patients with CML or Ph-positive ALL that could not tolerate or were resistant to imatinib.[31] This result led to the initiation of several phase II studies [SRC/ABL Tyrosine kinase inhibition Activity: Research Trials of dasatinib (START)] of dasatinib in patients with imatinib resistant or intolerant Ph-positive leukemias. Resistance to imatinib was defined as failure to achieve a complete hematologic response (CHR) within 3-6 months or absence of a McyR by month 12 or progression of disease after prior response. Dasatinib was administered at 70 mg twice daily on a continuous basis. Interruption of treatment and dose modifications were allowed for the management of disease progression or toxicity after one cycle of treatment.

In the START-C trial, patients with imatinib-resistant or intolerant chronic phase CML were treated with dasatinib (70 mg twice daily).[32] An initial result of this study for 186 patients revealed that CHR was observed in 90% of patients. Dasatinib also induced MCyR in 52% of the patients; only 2% of patients progressed or died after achieving MCyR. After a follow-up of 8 months, progression free survival rate was 92%. Extended 2-year follow-up data confirmed that dasatinib induces durable cytogenetic responses in patients with chronic phase CML. [33] After a follow-up of 24 months, CHR, MCyR, CCyR and MMR were observed in 91%, 62%, 53% and 47% of patients respectively. Overall and progression-free survivals at 24 months were 94% and 80% respectively. [33] Follow-up data reported by Baccarani and colleagues have confirmed the durability of cytogenetic responses with dasatinib.[34] At 2-years of follow-up, among imatinib-resistant patients, median time to MCyR and CCyR was 2.9 months and 5.5 months respectively. Among imatinib-intolerant patients, median times to achieve MCyR and CCyR were both 2.8 months. The majority of imatinib-resistant (84% for MCyR and 86% for CCyR) and imatinib intolerant patients (97% for MCyR and 98% for CCyR) had maintained their responses at 24 months.[34]

START-A trial evaluated the safety and efficacy of dasatinib (70 mg twice daily) in patients with imatinib resistant or intolerant accelerated phase CML.[35] At 8-month follow-up (for the first 107 patients enrolled in the study) major hematologic response (MaHR) was achieved in 64% of patients and MCyR was achieved in 33% of the treated population and 76% of patients remained progression-free. Follow-up data from the full patient cohort of 174 patients have confirmed the efficacy and safety of dasatinib in patients with imatinib resistant or intolerant accelerated phase CML.[36] The 12-month progression-free and overall survival rates were 66% and 82%, respectively.

The efficacy of dasatinib in imatinib resistant or intolerant patients with CML in myeloid blast crisis (MBC) or in lymphoid blast crisis (LBC) was evaluated in START-B and START-L trials respectively.[37] In patients with MBC-CML, 32% had achieved MaHR at 6-month follow-up, which increased to 34% at 8-month follow-up and this rate was maintained at 12-month follow-up.[38] MCyR was achieved in 31% of patients. In the LBC-CML group, 31% achieved MaHR at 6-month follow-up, and this rate increased to 35% at 12-month follow-up.[38] After a minimum follow-up of 12 months, MCyR was attained in 33% (MBP-CML) and 52% (LBP-CML) of patients and CCyR was attained in 26 and 46% of patients, respectively. Median PFS and OS for patients with MBC were was 6.7 and 11.8 months respectively. In patients with LBC, the corresponding survival rates were 3.0 and 5.3 months respectively. [38] Recently, 2-year follow-up data from a phase III trial showed that dasatinib 140 mg once daily demonstrates equivalent efficacy and improved safety compared with 70 mg twice daily in patients with CML in blast phase.[39]

Dasatinib induced cytogenetic and hematologic responses in significant number of patients with imatinib resistant CML (all phases), and was also well tolerated in all of these studies. Dasatinib was associated with significant but reversible inhibition of platelet aggregation that may contribute to bleeding in some patients receiving the drug.[40] Nonhematologic adverse events were mild to moderate and cytopenias although more common were manageable with dose modification. See “Management of Dasatinib Toxicity” in the guidelines.

Pleural effusion can be an adverse effect of dasatinib. Recently, Quintas-Cardama and colleagues from M.D. Anderson Cancer Center performed an analysis of patients with CML treated with varying doses of dasatinib in phase I and phase II studies.[41] Pleural effusion occurred in 29% of patients in chronic phase CML, 50% of patients with

accelerated phase CML and 33% of patients with blast phase CML. Pleural effusion led to dose interruption in 83% of patients and dose reduction was necessary in 71% patients with pleural effusion. Patients with prior cardiac history, hypertension and those receiving twice a day dosing of dasatinib at 70 mg are at increased risk of developing pleural effusion. Close monitoring and timely intervention is essential for continuation of treatment with dasatinib.

In June 2006, based on the favorable results of the above-mentioned four single-arm phase II studies, FDA approved dasatinib (70 mg twice daily) for use in patients with CML who are resistant or intolerant to imatinib.

In a recent dose-optimization randomized study, dasatinib dosed at 100 mg once daily was equally effective as 70 mg twice daily, and was also associated with a lower incidence of any grade pleural effusion (7% vs. 16%), and grade 3/4 thrombocytopenia (22% vs. 37%) in patients with chronic phase CML who were resistant or intolerant to imatinib.[42] Fewer patients required dose interruption (51% vs. 68%), dose reduction (30% vs. 55%) and toxicity-related discontinuation (16% vs. 23%). Based on the results of this study, FDA has approved 100 mg once daily as the starting dose. Four-year follow-up data confirmed the long-term safety and efficacy of dasatinib at 100 mg once daily. At 48 months, the PFS and OS rates were 66% and 82% respectively. The rate of progression to accelerated or blast phase was 4%.[43] Kantarjian et al recently reported that once daily dosing of dasatinib at 140 mg has similar efficacy to 70 mg twice daily dosing with an improved safety profile.[44]

The recommended starting dose is 100 mg once daily for patients with chronic phase CML resistant or intolerant to imatinib and 140 mg once daily for patients with disease progression to accelerated or blast phase CML.

The efficacy and safety of dasatinib as first-line therapy in previously untreated patients with chronic phase CML was first confirmed in a phase II trial.[45] Fifty patients with newly diagnosed early chronic phase CML were randomly assigned to dasatinib 100 mg once daily or 50 mg twice daily as initial therapy. With a median follow-up of 24 months, 98% of evaluable patients had achieved CCyR and 82% achieved MMR. In historical comparison, the CCyR rates at 3,6 and 12 months were comparable to those achieved with high dose imatinib and better than those achieved with standard dose imatinib.[45] There were no significant differences in response rate and toxicity between the two arms, and the median dose at 12 months was 100 mg.

The efficacy and safety of dasatinib (100 mg once daily) and imatinib (400 mg once daily) among patients with newly diagnosed chronic phase CML were compared in a multinational randomized study [The Dasatinib versus Imatinib Study in Treatment-Naive CML Patients (DASISION)], in which 519 patients with newly diagnosed chronic-phase CML were randomized to receive dasatinib (100 mg once daily; 259 patients) or imatinib (400 mg once daily; 260 patients).[46] After a minimum follow-up of 12 months, the rate of confirmed CCyR (77% vs. 66% respectively) and the rate of MMR (46% vs. 28%) were higher with dasatinib than with imatinib. Responses were achieved in a shorter time with dasatinib. The rates of CCyR at 3, 6 and 9 months after initiation of therapy were 54%, 73% and 78% respectively for dasatinib and the corresponding response rates were 31%, 59% and 67% respectively for imatinib. The rates of MMR at 3, 6 and 9 months after dasatinib treatment were 8%, 27% and 39% respectively and the corresponding rates for imatinib were 0.4%, 8% and 18% respectively. Progression to the accelerated or blastic phase occurred in 5 patients on dasatinib (2%) and in 9 patients who were

receiving imatinib (3.5%).[46] The safety profiles were similar in both treatment arms.

Nilotinib

Nilotinib (formerly known as AMN107) is a new orally available, highly selective inhibitor of BCR-ABL tyrosine kinase that is more potent than imatinib (20-50 times more potent in imatinib-resistant cell lines and 3-7 times more potent in imatinib-sensitive cell lines). In a phase I study, nilotinib was found to be active in imatinib resistant CML with a favorable safety profile.[47]

Following this study, a phase II open label trial evaluated the safety and efficacy of nilotinib in imatinib resistant or intolerant chronic phase and accelerated phase CML patients. Nilotinib was administered at 400 mg twice daily. The efficacy endpoint for chronic phase CML was MCyR and the endpoint for accelerated phase CML was MaHR. The results from an interim analysis conducted on 280 patients with chronic phase CML at 6-month follow-up were reported recently.[48] MCyR was observed in 48% of patients and CCyR was observed in 31% of patients. Long-term follow-up results from this study confirmed that these responses are durable with no change in safety profile.[49] At a minimum follow-up of 19 months, the overall MMR and CCyR rates were 28% and 46% respectively. MMR was higher in patients with CHR at study entry (38% vs. 22%). At 24 months, MCyR and CCyR were maintained in 77% and 84% of responding patients respectively. The estimated rates of PFS and OS at 24 months were 64% and 87% respectively. PFS rate was higher for patients with baseline CHR (77%) compared with patients without baseline CHR (56%).

In patients with accelerated phase CML, hematological response was observed in 47% of patients and MCyR was observed in 29% of patients.[50] Overall survival rate among the 119 patients after 12 months of follow-up was 79%. Non-hematologic adverse events were mostly mild to moderate. Grade 3 or higher bilirubin and lipase elevations occurred in 9% and 18% of patients. Long-term follow-up results confirmed that nilotinib induces rapid and durable responses with a favorable risk/benefit profile in patients with accelerated phase CML who were intolerant or resistant to prior imatinib.[49] Median duration of treatment was 272 days. Confirmed hematologic response was observed in 56% of patients and 31% had CHR (30% of imatinib-resistant and 37% of imatinib-intolerant patients achieved CHR). Median time to first hematologic response was one month and was durable at 24 months in 54% of patients. MCyR and CCyR were achieved in 32% and 20% of patients respectively. Cytogenetic responses were also durable with 70% of patients maintaining MCyR at 24 months and 83% of patients maintained CCyR at 12 months. Estimated OS at 24 months was 67%.

Nilotinib was rarely associated with fluid retention, edema or muscle cramps. Neutropenia and thrombocytopenia (grade 3-4) were reported only in 29% of patients with chronic phase CML. Grade 3 or 4 elevations in lipase and bilirubin, hypophosphatemia and hyperglycemia were observed in 17%, 8%, 16% and 12% of patients with chronic phase CML respectively. However, these abnormalities were transient and clinically asymptomatic. See “Management of Nilotinib Toxicity” in the guidelines.

QTc prolongation was a nonhematologic adverse reaction associated with nilotinib, which could be managed with dose reduction. Nilotinib labeling contains a black box warning regarding the risk of QT prolongation and sudden cardiac death has been reported in patients receiving nilotinib. Electrolyte abnormalities should be corrected prior to initiation of treatment with imatinib and should be monitored periodically. Drugs that prolong QT interval should be avoided.

Electrocardiograms (ECGs) should be obtained at baseline, periodically thereafter and as well as after any dose adjustment to monitor QTc. See “Important Considerations with Nilotinib” in the guidelines.

In October 2007, FDA approved nilotinib (400 mg twice daily) for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive CML in adult patients resistant to or intolerant to prior therapy with imatinib.

Nilotinib has also shown activity in a group of patients with blast phase CML. In a phase II study of 136 patients (82% imatinib-resistant and 18% imatinib-intolerant), nilotinib induced CHR in 13% of patients. MCyR were seen in 38% of patients with MBC and 52% of patients with LBC.[51] CCyR were seen in 30% of patients with MBC and 32% with LBC, respectively. Overall survival at 12 months was 42% and 27% at 24 months. However, the responses were not durable. The duration of MCyR was 11 months for patients with MBC and 3 months for those with LBC. Nilotinib is not yet approved by the FDA for the treatment of patients with blast phase CML.

The efficacy and the safety of nilotinib as first-line therapy in early chronic phase patients were initially evaluated in 2 separate phase II studies. Nilotinib at 400 mg twice daily induced high rates of CCyR and MMR, with most patients reaching these responses early during their therapy.[52, 53]

In a phase III, randomized, open-label, multicenter trial [Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients (ENESTnd) study, the efficacy and safety of nilotinib (300 mg or 400 mg twice daily) was compared with that of imatinib (400 mg once daily) in patients with newly diagnosed chronic phase CML.[54] At 12 months, the rates of MMR (the primary endpoint) were 44% for the 300-mg dose and 43% for the 400-mg dose vs. 22% for imatinib. The rates of CCyR by 12 months (80% for the 300-mg dose and 78% for the 400-mg dose vs. 65% for imatinib) were also higher for nilotinib than for imatinib.

Patients receiving nilotinib at either of the two dose levels had a significant improvement in the time to progression to the accelerated phase or blast crisis, as compared with those receiving imatinib. The rate of progression to accelerated or blast phase was 4% with imatinib and less than 1% with nilotinib. Among patients with a high Sokal risk, CCyR rates by 12 months were 74%, 63% and 49% among patients receiving 300 mg of nilotinib, 400 mg of nilotinib, and imatinib respectively. MMR at 12 months in these patients was 41%, 32% and 17% for patients receiving 300 mg of nilotinib, 400 mg of nilotinib, and imatinib respectively. The 300 mg dose of nilotinib had the lowest rate of discontinuation due to adverse events or laboratory abnormalities among the 3 study groups. Additional follow-up data will provide more information about the potential long-term effects of nilotinib as first-line therapy.

Based on the results of this study, in June 2010, FDA approved nilotinib (300 mg twice daily) for the treatment of adult patients with newly diagnosed Ph chromosome positive chronic phase CML.

TKI Therapy and Conception

Imatinib has been shown to be teratogenic and embryotoxic in animal studies. There are some reports in literature indicating that patients who receive imatinib at the time of conception may have normal pregnancies.[55-62] Pye and colleagues recently reported the outcome of pregnancies in 180 women exposed to imatinib during pregnancy. Fifty percent of pregnancies with known outcome were normal and 10% of pregnancies with known outcome had fetal abnormalities.[61] Eighteen pregnancies ended in spontaneous abortion. In another report by Ault

and colleagues, of the 10 women who discontinued imatinib due to pregnancy, six had an increase in Ph-positive metaphases. Only three women had CCyR, at 18 months after resuming therapy.[57] Imatinib is not known to be a genotoxic. However, spermatogenesis was impaired in animal studies. In the clinical experience, male fertility seems to be preserved in patients receiving imatinib.[61, 62] However, there are isolated reports of oligospermia in men receiving imatinib therapy.[63]

Dasatinib and nilotinib are known to cause embryonic or fetal toxicities in animals. There have been isolated reports in literature regarding the outcome of pregnancy in patients receiving dasatinib [64-66] or nilotinib.[67] In a report from Cortes and colleagues involving 16 patients, among the 8 female patients who became pregnant while on dasatinib, induced or spontaneous abortion was reported in 3 and 2 patients respectively. The outcome and pregnancy course in other three patients were normal.[64] Among the 8 male patients treated with dasatinib whose partners became pregnant while on treatment, normal pregnancy was reported for 7 cases and the outcome was unknown in one case.[64]

At the present time, enough evidence is not available to favor the continuation of imatinib, dasatinib or nilotinib during pregnancy. Potential benefit of TKI therapy for the mother or its potential risk to the fetus must be carefully evaluated on an individual basis prior to administering imatinib, dasatinib or nilotinib for pregnant women. Men desiring conception should consider sperm cryopreservation prior to initiation of TKI therapy.

Drug Interactions

Imatinib

Imatinib is predominantly metabolized in the liver by the cytochrome P 450 enzymes, CYP3A4 or CYP3A5.[68] Drugs that induce CYP3A4/5 enzyme levels may decrease therapeutic levels of imatinib. CY3A4/5-inducing drugs such as anticonvulsants and steroids should be used with caution in patients receiving imatinib, and appropriate alternatives should be explored to maximize treatment outcome. Conversely, drugs that inhibit CYP3A4 enzyme activity and drugs that are metabolized by the CY3A4/5 enzyme might result in increased plasma levels of imatinib. Imatinib is also a weak inhibitor of the CYP2D6 and CYP2C9 isoenzymes; therefore, drugs metabolized by these enzymes (eg. warfarin) should be used with caution. Please refer to the package insert for full prescribing information and drug interactions, available at www.fda.gov.

Dasatinib

Dasatinib is extensively metabolized in the liver, primarily by CYP3A4. CYP3A4 inducers may decrease plasma concentration of dasatinib. CYP3A4 inhibitors and drugs that are metabolized by this enzyme may increase the concentration of dasatinib. Therefore, concomitant administration with CYP3A4 inhibitors or inducers should be avoided. If coadministration cannot be avoided, a dose adjustment and close monitoring for toxicity should be considered. In addition, the solubility of dasatinib is pH-dependent, and long-term suppression of gastric acid secretion reduces dasatinib exposure. Concomitant use with H2 blockers or proton pump inhibitors (PPIs) is not recommended. Please refer to the package insert for full prescribing information and drug interactions, available at www.fda.gov.

Nilotinib

Nilotinib is also metabolized by the CYP3A4 isoenzyme and drugs that induce CYP3A4 may decrease nilotinib plasma concentrations. If nilotinib needs to be administered with a CYP3A4 inducer, dose increase should be considered. Concomitant administration of strong inhibitors of CYP3A4 may increase the concentration of nilotinib. If coadministration cannot be avoided, nilotinib should be interrupted or

dose reduction should be considered. In addition, nilotinib is a competitive inhibitor of CYP2C8, CYP2C9, CYP2D6, and UGT1A1, potentially increasing the concentrations of drugs eliminated by these enzymes. Please refer to the package insert for full prescribing information and drug interactions, available at www.fda.gov.

Chronic Phase CML

Initial Workup

The panel recommends the following tests as part of the initial evaluation of patients with chronic phase CML:

- History and physical (H&P) including spleen size by palpation
- Complete blood count (CBC)
- Platelet count
- Chemistry profile
- Bone marrow aspirate and biopsy

Bone marrow cytogenetics and measurement of *BCR-ABL* transcript levels by quantitative reverse transcriptase polymerase chain reaction (QPCR) is recommended before initiation of treatment as well as for assessing the response to therapy.[69]

Conventional bone marrow cytogenetics is recommended for initial work-up since it not only to provide morphologic review, but also detects chromosomal abnormalities other than Ph-chromosome that not detectable using peripheral blood. If collection of bone marrow is not feasible, FISH on a peripheral blood specimen with dual probes for BCR and ABL genes is an acceptable method for confirming the diagnosis of CML.

Patients who are *BCR-ABL*-negative do not have CML. These patients have a significantly worse prognosis than those with *BCR-ABL*-positive disease.[70] Therefore, further evaluation for other diseases is warranted for patients with *BCR-ABL*-negative disease. Patients whose cells are *BCR-ABL*-positive (by karyotype analysis, FISH or molecular techniques) are the focus of this NCCN guideline.

Primary Treatment

Imatinib is recommended for newly diagnosed patients with Ph chromosome or *BCR-ABL* positive chronic phase CML. Based on the recent FDA approval of nilotinib and the clinical trial data for dasatinib, the guidelines have also included nilotinib or dasatinib for newly diagnosed patients. Imatinib (400 mg once daily) or nilotinib (300 mg twice daily) or dasatinib (100 mg once daily) are listed as options with a category 1 recommendation for initial treatment of CML.

The NCCN participating centers believe that interferon should no longer be considered as initial therapy for CML, given the excellent long-term results with imatinib. In patients treated with interferon, 10-15% achieved a CCyR with a median survival of more than 10 years; some of these patients may actually be cured. However, given this small percentage, most of the panel believed that this data for interferon did not outweigh the significant benefits seen with imatinib. In very rare patients who are not able to tolerate TKI therapy, interferon or PEG-interferon therapy, allogeneic hematopoietic stem cell transplant (HSCT) or participation in a clinical can be considered. In phase II/III studies, pegylated interferon-alpha 2a and alpha 2b have been shown to be active as initial treatment in patients with chronic phase CML.[71, 72]

Resistance to Imatinib

Primary Resistance

Primary hematologic resistance to imatinib therapy (failure to achieve hematologic remission within 3 to 6 months of initiation of treatment) is very rare in newly diagnosed patients with Ph-positive chronic phase

CML, whereas primary cytogenetic resistance (failure to achieve any level of cytogenetic response at 6 months, MCyR at 12 months or CCyR at 18 months) is evident in 15% to 25% of patients.

Imatinib plasma levels

Available data indicate that inadequate plasma concentration of imatinib may be one of the causes for primary resistance.[73-75] Gambacorti-Passerine and colleagues observed that excessive binding of imatinib to plasma protein AGP (alpha-1-glycoprotein) may reduce the therapeutic effect of imatinib.[73] Picard and colleagues also observed that trough plasma levels of imatinib were significantly higher in patients achieving CCyR and MMR at 12 months.[75] In a subanalysis of the IRIS study, plasma levels of imatinib following the first month of treatment proved to be a significant prognostic factor for long-term clinical response.[74] However, other investigators have suggested that plasma levels of imatinib in patients receiving different dose schedules had no correlation with response to therapy.[76, 77]

The clinical value of monitoring plasma levels of imatinib remains to be defined. Monitoring imatinib plasma levels may be useful in determining patient adherence to therapy. However, at the present time, there is no data to support that change of therapy based on plasma imatinib levels will affect treatment outcomes. Therefore, the panel does not recommend routine imatinib plasma level testing.

Intracellular concentration of imatinib

Aberrant expressions of drug transporters also contribute to resistance by altering the intracellular concentration of imatinib. Overexpression of the multidrug resistance gene (*MDR1)* decreases the intracellular concentration of imatinib, which may confer resistance to imatinib.[78] Pretreatment levels of human organic cation transporter-1 (hOCT1) have been reported as the most powerful predictor of response to imatinib.[79] White and colleagues recently reported that most patients with suboptimal response to imatinib have low hOCT1 activity.[80] In the updated analysis of patients enrolled in the TIDEL trial, MMR rate at 60 months was higher for patients with high OCT-1 activity compared to those with low hOCT1 activity (89% vs. 55% respectively). Low hOCT1 activity was also associated with a significantly lower overall (87% vs. 96%) and event-free survival (48% vs. 74%) as well as a higher kinase domain mutation rate (21% vs. 4%). These differences were highly significant in patients who averaged less than 600 mg/day of imatinib.[81] On the other hand, cellular uptake of dasatinib or nilotinib seems to be independent of hOCT1 expression.[82-85] Thus, preliminary findings suggest that patients with low hOCT1 expression might have better outcomes with dasatinib or nilotinib**.**

Secondary Resistance

The most common mechanism for secondary resistance is the reactivation of *BCR-ABL* activity. This occurs most often by mutations in the ABL tyrosine kinase domain of *BCR-ABL* gene (resulting in conformational changes in the fusion protein that affect the binding site of imatinib on the tyrosine kinase) and less frequently by *BCR-ABL* gene amplification, or increased *BCR-ABL* gene expression.[86-88] In the START-C study, 46% of patients with imatinib-resistant chronic phase CML did not carry *BCR-ABL* mutations confirming that secondary resistance to imatinib is multifactorial. Other mechanisms that are independent of *BCR-ABL* include activation of the Src family of kinases (SFKs) or cytogenetic clonal evolutions characterized by additional chromosomal abnormalities in the Ph-positive cells.[87, 89]

Point mutations in the ABL kinase domain are emerging as the most frequent mechanism of resistance. In a large study of 319 chronic phase patients, Khorashad et al found that kinase domain mutations were the only independent predictor for the loss of CCyR and a higher

risk progression (3.8 and 3.7-fold, respectively) when compared to patients without a mutation.[90] Patients with P-loop mutations were associated with a particularly high risk of progression. Other studies have also reported that mutations in the ATP phosphate-binding loop (P-loop) are associated with poor prognosis and high risk of progression among patients treated with imatinib.[91-94] However, Jabbour and colleagues could not confirm these findings.[95] In the START trials, dasatinib induced similar rates of major hematological and cytogenetic responses irrespective of the presence of P-loop or other mutations, in imatinib resistant patients with accelerated or blast phase CML.[35, 37] Branford and colleagues observed that although there was a higher incidence of P-loop mutations in the accelerated phase, the difference in the frequency of mutation was significant between early chronic phase and accelerated phase, compared to that between accelerated phase and late chronic phase.[91]

Among the mutations in the ABL kinase domain, the presence of T315I mutation confers the highest resistance to imatinib, dasatinib and nilotinib. Some reports have suggested that T315I is associated with disease progression and poor survival.[96, 97] Jabbour and colleagues reported that survival of patients with T315I is dependent on the stage of the disease, with many chronic phase patients having an indolent course.[96] Patients in chronic phase had a 2-year survival rate of 87%. In patients in the accelerated phase and blast phase, survival rates were similarly poor irrespective of their T315I mutational status.

Clonal evolutions are considered to be a feature of accelerated phase CML. In patients with accelerated phase, clonal evolution resulted in lower response rates and a shorter time to treatment failure. However, in a subset of patients, clonal evolution was associated with a better prognosis when it was considered as the only criteria for accelerated phase disease.[98] With a median follow-up of 12 months, the MCyR and CCyR rates were 73% (11 of 15) and 60% (9 of 15) respectively. In a subsequent report, of 141 patients treated with imatinib after failing interferon, O'Dwyer and colleagues identified clonal evolution, an elevated platelet count and failure to achieve MCyR by 6 months as adverse prognostic factors for hematologic relapse.[99]

In a study from M.D. Anderson Cancer Center (prior to the use of imatinib), Majlis and colleagues analyzed patients who developed cytogenetic clonal evolution on interferon therapy. They concluded that the prognostic significance of clonal evolution is not uniform, but it is related to the specific chromosomal abnormality and the presence of other features of accelerated phase.[100] In this study, presence of chromosome 17 abnormality, predominance of abnormal metaphases (36% or more) and the other accelerated features were identified as the worst prognostic factors. In a large trial of 498 patients in chronic or accelerated phase, cytogenetic clonal evolution was not an important factor for achieving MCyR or CCyR with imatinib, but it was an independent poor prognostic factor for survival in both chronic and accelerated phases of CML.[101] In patients with chronic phase CML failing imatinib and treated with second-generation TKIs, the hematologic and cytogenetic response rates, OS, and EFS were not different between patients in chronic phase with clonal evolution and those with no clonal evolution.[102] However, clonal evolution had a significant adverse impact when associated with other features of accelerated phase. Patients with cytogenetic abnormalities including trisomy 8, chromosome 17, and complex abnormalities had the worst outcome, regardless of the number of metaphases involved.

Clonal cytogenetic abnormalities in Ph-negative cells have also been reported in a small subset of patients during the course of imatinib therapy.[103-106] The significance of these chromosomal abnormalities is unclear, but the most common abnormalities include trisomy 8, an

aberration frequently seen in myelodysplastic syndrome. Only rare cases of myelodysplastic syndrome or AML have been reported in patients with CML and these were usually in patients who had received interferon as well as prior chemotherapy. Some of these abnormalities may persist only in a small percentage of metaphases or they may be transient and disappear with continued therapy in patients who have achieved CCyR. In a recent report, Deininger and colleagues concluded that the overall prognosis for patients with Ph-negative CML and clonal cytogenetic evolution was good and was dependent on their response to imatinib therapy.[107] In newly diagnosed patients with chronic phase CML treated with imatinib, chromosomal abnormalities in Ph-negative cells appeared in 9% of the patients.[108] Loss of Y chromosome was most common. The significance of loss of Y chromosome in this setting is unclear. It has been reported that this phenomenon is a common occurrence in male individuals with aging.

Taken in full, the data suggest that mutational analysis would be helpful in identifying a subgroup of patients that demand careful monitoring as these patients are at a higher risk of progression. Mutational analysis would also be helpful to identify the subset of patients who will be eligible for allogeneic HSCT.

Management of Resistance

Dose escalation of imatinib up to 800 mg daily has been shown to overcome some of the primary resistance, but the duration of responses has typically been short.[109-111] Jabbour and colleagues assessed the long-term efficacy of imatinib dose escalation after hematologic or cytogenetic failure in 84 patients with chronic phase CML.[112] After a median follow-up of 61 months, the estimated 2- and 3-year EFS and OS rates were 57% and 47% and 84% and 76% respectively. Responses were also durable; 88% of patients with MCyR sustained their response beyond 2 years. Dose escalation was particularly effective in patients with cytogenetic relapse who had achieved cytogenetic response with standard dose imatinib. In this group of patients, CCyR and MCyR rates were 73% and 87% respectively, compared to 52% and 60% for the overall group of patients with cytogenetic failure. These results indicate that dose escalation of imatinib is unlikely to benefit those with hematologic failure or those who never had a cytogenetic response with standard dose imatinib. Kantarjian et al performed a retrospective analysis of 106 patients with newly diagnosed chronic phase CML from the IRIS trial, who received imatinib at a dose of 400 mg daily, and subsequently underwent dose escalation to either 600 mg or 800 mg daily.[113] The rates of FFP to accelerated or blast phase and OS were 89% and 84% at 3 years after dose increase, respectively. The results of this retrospective analysis also supported that dose escalation of imatinib is an appropriate option for patients in chronic phase who were experiencing suboptimal cytogenetic response or cytogenetic relapse.

Dasatinib and nilotinib have been effective in patients with imatinib resistant or intolerant chronic phase CML. The efficacy of high dose imatinib and dasatinib were evaluated in a phase II trial (START-R) in which 150 patients with imatinib resistant chronic phase CML were randomized to receive 140 mg (70 mg twice a day) of dasatinib or 800 mg of imatinib.[114] At a minimum follow-up of 2 years, dasatinib demonstrated higher rates of CHR (93% vs 82%), MCyR (53% vs 33%), and CCyR (44% vs. 18%) compared to high dose imatinib. MMR was also more frequent with dasatinib than with high-dose imatinib (29% vs. 12%) and the estimated progression-free survival also favored dasatinib, indicating that dasatinib is an effective treatment for patients with chronic phase CML resistant to conventional imatinib doses. However, response rates were equivalent for high dose imatinib and

dasatinib in patients who had failed treatment with 400 mg of imatinib, whereas dasatinib was clearly superior to 800 mg of imatinib if they had already failed 600 mg of imatinib.[115]

Several new agents under clinical development have shown promising results in the management of patients with T315I mutation.[116] Recently, some studies have reported the clinical activity of omacetaxine (OMA; homoharringtonine) in patients with CML after imatinib failure including those with BCR-ABL kinase domain mutations.[117, 118] In two long-term phase II studies, omacetaxine induced hematologic and cytogenetic responses in patients with T315I mutation who had failed imatinib (CML-202; n =81)[119] and in patients who were intolerant or resistant to 2 or more TKIs (CML-203; n=89).[120] Preliminary results of CML-202 study showed that among 44 evaluable patients, the T315I clone was reduced to below detection limits in 64% of patients. In patients with chronic phase CML, CHR and CCyR were seen in 80% and 16% of patients and 28% respectively. Median duration of CHR and CCyR was 12 and 5 months respectively. The estimated 2-year PFS was 70%.

Monitoring Response to Imatinib

Disease monitoring to assess the response to therapy and to detect early relapse is one of the key management strategies of CML.[121,122, 123] There are 3 different types of responses in CML: hematologic, cytogenetic and molecular response. See Criteria for Cytogenetic, Hematologic and Molecular Response" in the guidelines. A widely accepted goal of CML therapy is to achieve CCyR within 18 months of initiation of therapy.

Hematologic Response

CHR is defined as complete normalization of peripheral blood counts with no immature blood cells, leukocyte count less than 10 x 10^9/L and the platelet count less than 450 x 10^9/L. The patient is free of signs and symptoms of the disease with the disappearance of splenomegaly. Partial hematologic response indicates the presence of immature blood cells and/or platelet count less than 50% of pretreatment count but more than 450 x 10^9/L and/or persistent splenomegaly (but less than 50% of pretreatment).

Cytogenetic Response

Cytogenetic response is determined by the decrease in the number of Ph-positive metaphases, as determined by bone marrow aspirate and cytogenetic evaluation. Cytogenetic monitoring is the most widely used technique for monitoring response in patients with CML. CCyR indicates that there are no Ph-positive metaphases. MCyR indicates that 0% to 35% of the cells still have Ph-positive metaphases and in the case of partial cytogenetic response 1% to 34% of the cells have Ph-positive metaphases.

Conventional cytogenetics for Ph-positive metaphases is the standard for monitoring cytogenetic responses in CML and clinical trial response analyses are most often based on standard cytogenetics. It is widely available and reliable. However, the sensitivity is approximately 5% if only 20 metaphases are examined. If conventional cytogenetics showed no analyzable metaphases, cytogenetic response can be further evaluated by more sensitive techniques such as FISH although endpoints for failure to imatinib have been defined on the basis of FISH analysis.[124, 125] FISH uses 5'-*BCR* and 3'-*ABL* probes and has a false positive rate of 1% to 10%. Interphase or hypermetaphase FISH can be performed on peripheral blood specimens or marrow aspirates, respectively. Interphase FISH does not require cell division. It is applicable to a larger number of cells but is associated with a background level of 1-5% (depending on the specific probe used in the

assay).[126] Hypermetaphase FISH is applicable only to dividing cells in the bone marrow. Hypermetaphase FISH is more sensitive and can analyze up to 500 metaphases at a time.[127] Techniques such as double-FISH (D-FISH) can detect all variant translocations of the Ph-chromosome and are also associated with low false positive rates.[128] FISH can be used complimentary to conventional cytogenetics until FISH levels are less than 5% to10%. This technique is no longer useful for monitoring further reduction in Ph levels. At this point, more sensitive techniques are required.

Cytogenetic responses are indicative of treatment effectiveness. In the IRIS study, progression-free survival (PFS) was significantly better for patients who achieved any cytogenetic response at 6 months and a MCyR at 12 months, compared to those with no cytogenetic response at 6 months or less than a MCyR at 12 months. At the median follow-up of 60 months, PFS rate was better for patients who achieved a CCyR or a partial cytogenetic response at 12 months compared to those who did not have a MCyR at 12 months (97%, 93% and 81% respectively).[13] At 8-years, of the 456 patients who achieved CCyR on imatinib, only 15 patients (3%) had progressed to accelerated or blast phase during study treatment.[14] de Lavallade and colleagues also identified cytogenetic response after 1 year of imatinib therapy as the major prognostic factor for overall survival (OS) and PFS.[129] In the retrospective analysis of data from phase II studies of dasatinib in imatinib-resistant chronic phase CML patients, EFS was higher for those who went on dasatinib after losing MCyR on imatinib than those who received dasatinib after the loss of both MCyR and CHR (89% and 29% respectively).[130]

The updated results of the IRIS trial confirmed that patients with minor cytogenetic response at 3 months, partial cytogenetic response at 6 and 12 months and CCyR at 18 months were associated with stable CCyR over the observation period. Patients with minor to partial cytogenetic response at 3 months and those with partial cytogenetic response at 6 and 12 months were more likely to achieve a stable CCyR than have an event.[14]

In the guidelines, cytogenetic evaluation is recommended at 6, 12 and 18 months following imatinib therapy. If there is a persistent, unexplained, drop in blood counts during therapy, it may be reasonable to perform a bone marrow and cytogenetic evaluation to look for non-Ph clonal changes and evidence of myelodyplasia.

Molecular Response

Molecular response is determined by the decrease in the amount of *BCR-ABL* chimeric mRNA. Complete molecular response (CMR) occurs when there is no detectable *BCR-ABL* chimeric mRNA as assessed by RT-PCR. MMR indicates that there is a reduction (3-log reduction or greater) of *BCR-ABL* chimeric mRNA.

RT-PCR (reverse transcriptase polymerase chain reaction) is the most sensitive assay available for the *BCR-ABL* chimeric mRNA. This assay measures the levels of *BCR-ABL* transcripts in the peripheral blood or in the bone marrow, and it can detect one CML cell in a background of ≥100,000 normal cells. The majority of patients initially treated with imatinib or allogeneic HSCT will achieve a CCyR, however a smaller percentage will achieve a CMR identified by the absence of *BCR-ABL* mRNA transcripts. The *BCR-ABL* mRNA transcripts typically fall slowly after complete cytogenetic remission is reached. Therefore, RT-PCR assays are useful to establish a baseline *BCR-ABL* for monitoring molecular responses after the patient has achieved CCyR.

Qualitative RT-PCR technique is reported as either positive or negative; it is rarely used in the context of monitoring patients since it

is only a “yes or no” answer. In contrast, a quantitative RT-PCR assay (QPCR) reports the actual percentage of *BCR-ABL* mRNA transcripts.[131] A major advantage of QPCR testing is the strong correlation between results obtained from the peripheral blood and the bone marrow, allowing molecular monitoring without the necessity for obtaining bone marrow aspirations. Amongst institutions and laboratories that perform this test there are differences in techniques as well as the use of various internal controls that make quantification of the assay variable. A substantial effort has been made to standardize the *BCR-ABL* testing and reporting across academic and private laboratories.[132-135]

In the QPCR assay, results are expressed as the ratio of *BCR-ABL* transcript numbers to the number of control gene transcripts. Thus, the choice of an appropriate control gene is important for generating reliable and reproducible data. *BCR, ABL,* beta glucuronidase *(GUSB)* and beta-2-microglobilin (*B2M)* are the 4 control genes that have been widely studied for *BCR-ABL* quantification. In 2006, the National Institute of Health Consensus group proposed an international scale (IS) for *BCR-ABL* measurement.[135] This group recommended the use of one of three control genes-*BCR, ABL* or *GUSB.* In the IRIS trial, *BCR* was used as the control gene and the standardized baseline was calculated by measuring the level of *BCR-ABL/BCR* in the peripheral blood collected from 30 patients with newly diagnosed chronic-phase CML prior to the initiation of any treatment.[136] The same 30 samples were assayed in the 3 laboratories. The median value was used as the standardized base line at each laboratory and at least a 3-log reduction from this baseline was defined as the MMR. Thus, MMR is defined as a 3-log reduction in the *BCR-ABL* transcript levels from the standardized baseline and not a reduction from the actual baseline level in an individual patient.

Several studies have reported the prognostic significance of molecular response.[137] MMR is associated with durable long-term remission rates and PFS after treatment with imatinib. The 5-year follow-up of the IRIS trial showed that no patient who had a CCyR and a MMR at 12 months had progressed to the accelerated or blast phase.[13] The estimated PFS rate at 24 months was 100% for patients with a CCyR and at least a 3-log reduction in the *BCR-ABL* transcript level at 12 months, compared to 95% for those with CCyR and a less than 3-log reduction of *BCR-ABL* at 12 months. The 6-year follow-up of the IRIS study also showed that progression is very rare in patients who achieved MMR at any time point during imatinib therapy. The estimated EFS rate at 72 months was 98% for patients who had a MMR at 18 months compared to 89% in those with no MMR at this time point.[138] Press and colleagues also reported that failure to achieve at least a 2-log reduction in *BCR-ABL* mRNA at the time of CCyR or a 3-log reduction any time thereafter is associated with a significantly shorter PFS [139] and a minimal half-log increase in the *BCR-ABL* or a loss of MMR predicts shorter relapse-free survival in patients who were in complete cytogenetic remission on imatinib therapy.[140]

Molecular responses also predict the duration of CCyR. Cortes et al reported that significantly lower portion of patients (5% with MMR and 4% with complete molecular remission) lost their CCyR compared to 37% who did not reach these levels of molecular response.[141] The GIMEMA study group reported similar findings.[142] Although early molecular response is a predictor of durable long-term remission rates and PFS, some studies suggest that it does not predict a long-term survival advantage. In patients achieving CCyR at 12 months or 18 months, achievement of molecular response at these time points did not affect PFS or OS.[129] Marin et al also confirmed that even though

patients who did not have a MMR at 18 months had a higher chance of losing CCyR, this did not translate into difference in PFS.[143]

Rising *BCR-ABL* levels

Several studies have shown that a rising *BCR-ABL* level may be associated with an increased risk of *BCR-ABL* mutations in the future.[144-147] Brandford and colleagues reported that in patients who had achieved very low levels of *BCR-ABL* transcripts, emergence of *BCR-ABL* mutations was more frequent in those who had more than a 2-fold increase in *BCR-ABL* levels compared to those with stable or decreasing *BCR-ABL*.[144] In contrast, Wang reported that a serial rise is more reliable than a single 2-fold or greater rise in BCR-ABL transcript levels.[145] In an analysis of 258 patients with chronic phase CML on imatinib therapy, Kantarijian et al studied 116 patients in CCyR and that experienced an increase in *BCR-ABL* transcript levels of half log or more on at least two occasions.[146] Eleven of 116 (9%) had CML progression. The patients with the highest risk were those that lost MMR with a greater than one log increase in *BCR-ABL*, or those who never achieved a MMR and had a one log rise in *BCR-ABL*.

The amount of *BCR-ABL* increase that warrants concern, and should trigger mutation testing, is not known. Some labs have advocated a 2-3 fold range,[144,147] while others have taken a more conservative approach (0.5-1 log). Obviously, some common sense must prevail, since the amount of change in absolute terms depends on the MMR level. For example, a finding of any *BCR-ABL* compared to CMR is an infinite increase in *BCR-ABL* level, though a change from CMR to a barely detectable level is clearly different than a five-fold increase in a case hovering at the MMR level.

Currently there are no specific guidelines for changing therapy based on rising *BCR-ABL* transcripts as detected by QPCR. Changes of therapy based solely on a rising *BCR-ABL* level should be done only in the context of a clinical trial.

Mutational Analysis

Dasatinib and nilotinib are active against many of the imatinib-resistant BCR-ABL kinase domain mutations, except T315I. Available clinical evidence indicates that in addition to T315I, mutations F317 and V299 are resistant to dasatinib and mutations Y253H, E255 and F359 are resistant to nilotinib.[148] The IC50 values for TKIs against various *BCR-ABL* mutations are given in Figure 1.

Muller et al recently reported the results of the largest analysis of clinical response to dasatinib after imatinib failure in 1043 patients with chronic phase CML according to the preexisting *BCR-ABL* mutations.[149] The presence of T315I and F317L mutations at baseline was associated with less favorable responses. A few responses (CHR and MCyR) were observed in patients with T315I mutation but no CCyRs. Patients with an F317L mutation had a high rate of CHR (93%), but low rates of MCyR and CCyR (14% and 7% respectively) whereas favorable CCyR rates were achieved in patients with highly imatinib-resistant mutations such as E255K/V (38%), and L248V (40%). Other studies have also reported similar findings in patients with F317 mutations at baseline.[150, 151] In one study, F315 and/or F317 mutations were associated with resistance to dasatinib.[151] In another study, patients with F317L mutation had a similar survival compared with patients with other mutations with outcome dependent on the CML phase and this mutation was sensitive to other TKIs.[150]

Hughes et al assessed the occurrence and impact of baseline *BCR-ABL* mutations on nilotinib therapy in patients with imatinib resistant chronic phase CML.[152] Patients with Y253H, E255V/K,

F359V/C mutations achieved less favorable MCyR rates (13%, 43%, and 9% respectively) and none of them achieved CCyR within 12 months of therapy. E255K/V, F359C/V, Y253H, and T315I mutations were most commonly associated with disease progression. Consistent with these findings, F359V, Y253H and E255K/V mutations were associated with relapse to nilotinib in the study reported by Soverini et al.[153]

Branford and colleagues studied a large sample of imatinib-resistant patients with *BCR-ABL* mutations, and found that of patients with mutations, clinically relevant mutations less sensitive to nilotinib (Y253H, E255K/V, and F359V/C) or dasatinib (F317L and V299L) or both (T315I) occurred in 43% of cases including 14% with T315I.[148]

Identification of mutations supports the diagnosis of imatinib resistance. Patient's mutation status at the time of loss of response to first generation TKI may be helpful in selection of subsequent TKI therapy.

NCCN Recommendations

Monitoring Response to First-line TKI Therapy and Mutational Analysis

Most patients receiving TKI therapy will achieve a CHR at 3 months, CCyR at 6, 12 or 18 months. If there is no hematologic and cytogenetic response at the above-mentioned intervals, mutational analysis should be considered and patient compliance to TKI therapy should be evaluated. Since there are no data regarding the time points for monitoring response to dasatinib or nilotinib, at the present time, the panel believes that the same evaluation points recommended for monitoring response to imatinib could be applied to dasatinib or nilotinib as well. The optimal guidelines for monitoring response to TKI therapy and mutational analysis are outlined in Table 2.

Follow-up Therapy

Patients not responding to first-line therapy with a second-generation TKI should be switched to the other second-generation TKI (that they have not received before) for second-line therapy. Participation in a clinical trial or allogeneic HSCT is a reasonable treatment option for patients with T315I mutation, since this mutation is associated with resistance to imatinib, dasatinib and nilotinib. The recommendations for follow-up therapy are outlined in Table 3.

Monitoring Response to Second-line TKI Therapy

Early cytogenetic response to second-line TKIs can predict survival and guide subsequent therapy.[154,155] Tam and colleagues reported that in patients receiving dasatinib or nilotinib, patients achieving MCyR after 12 months of treatment had a significant advantage over those achieving minor cytogenetic response or CHR. [154] Milojkovic and colleagues also reported that among patients with chronic phase CML who were resistant to imatinib and who were treated with dasatinib or nilotinib, those who had a minimal cytogenetic response at 3 months, partial cytogenetic response at 6 months and CCyR at 12 months had significantly better outcomes than patients with lesser degrees of cytogenetic response. At the 12- month landmark analysis, patients with a CCyR at 12 months had significantly superior event-free (97% vs. 80%) and overall survival (100% vs. 85%) probabilities compared to those who had failed to achieve a CCyR. There were no significant differences in progression-free survival. More recently, Shah et al reported that response to dasatinib 100 mg once daily at 6 and 12 months was predictive of PFS at 48 months. The PFS rate after 48 months was higher for patients who achieved CCyR at 6 months compared to those who were in partial cytogenetic response (93% and 67% respectively).[43] Similarly, PFS rate was 87% for those with a CCyR (with or without MMR) at 12 months compared to 78% and 45%

respectively for those with partial cytogenetic response or no cytogenetic response at 12 months. Thus, patients receiving dasatinib or nilotinib with no cytogenetic response at 3 or 6 months should be considered for alternative therapies.

The measurement of *BCR-ABL* transcript level at three months following second-line TKI therapy has also been reported to be predictive of response and may provide further information about the value of continuing treatment with the second generation TKIs.[155-157] In imatinib-resistant and intolerant patients receiving nilotinib, *BCR-ABL*% (IS) at 3 months correlated with MCyR, MMR and EFS rates regardless of baseline mutation.[157] Patients whose *BCR-ABL* % (IS) levels decreased below 10% at 3 months have a high probability of achieving MMR and MCyR at 24 mos. Similarly, patients who achieve early molecular response may also have an increased probability of improved long-term outcomes on nilotinib therapy, while patients with *BCR-ABL*% (IS) value of greater than 10 at 3 months may have a poorer prognosis.
The use of a second-generation TKI after failure of 2 prior TKIs may induce responses in some patients, but these are not durable except in occasional patients in chronic phase.[158] Investigational therapies or allogeneic HSCT should be considered for this group of patients.

Discontinuation of TKI Therapy

Imatinib has become a standard front-line treatment for patients with CML. CCyR can be achieved in most patients with chronic phase CML. The results of the IRIS study suggest that the annual mortality rate among patients with CML receiving imatinib is less than 5% in the first 5-6 years of treatment compared to 10-20% in the pre-imatinib era and patients responding to imatinib are likely to maintain their responses on long-term therapy.[14, 159] However, the disease usually relapses if imatinib therapy is stopped even in patients who achieved complete response.[160] In a pilot study (n=12), Rousselot and colleagues have suggested that discontinuation of imatinib is feasible in a subset of patients achieving sustained CMR.[161] Most of the patients (10 of 12) in this study had received prior interferon therapy. Ross et al also concluded that imatinib withdrawal in patients with stable CMR is safe with close molecular monitoring.[162] However, the sample size was small (n=18) and follow-up was short.

A multicentre Stop Imatinib (STIM) study evaluated the persistence of complete molecular remission after discontinuation of imatinib in 50 patients (25 of these had no prior interferon treatment). In this study more than half of the patients who were not pretreated with interferon had not relapsed, confirming that it is possible to stop treatment in patients with sustained CMR even in those treated with imatinib alone.[163] Updated results of this study confirmed these findings particularly in male patients, those with a low Sokal score, and in patients with cytotoxic NK cells in the peripheral blood prior to discontinuation of imatinib.[164] Thus, investigators recommend that withdrawal of imatinib should be done only in the setting of a clinical trial.

In the absence of data from studies evaluating the probability of discontinuing dasatinib and nilotinib in responding patients, the findings from the studies involving patients treated with imatinib could be extrapolated to these drugs also. Additional prospective studies are needed to determine the optimal duration of TKI therapy in patients who are in complete molecular remission. At the present time, discontinuation of TKI therapy is not recommended outside the context of a clinical trial for patients who are responding to TKI therapy.

Patient Adherence to TKI Therapy

Treatment interruptions and non-adherence to TKI therapy may lead to undesirable clinical outcomes.[165-167] In the ADAGIO (Adherence Assessment with Glivec: Indicators and Outcomes) study which evaluated the outcomes of non-adherence to imatinib therapy in patients with CML, non-adherence was associated with poorer response to imatinib. Patients with suboptimal response had significantly higher mean percentages of imatinib not taken (23%) than did those with optimal response (7%).[167] Marin and colleagues recently identified adherence as the only independent predictor for achieving CMR on standard dose imatinib.[166] Patients whose imatinib doses were increased had poor adherence (86%) and in these patients, adherence was the only independent predictor for inability to achieve an MMR. Although the effects of non adherence to dasatinib and nilotinib have not been reported yet, Marin and colleagues suggest that the findings from the above studies may apply equally to patients receiving these drugs as well.

Patient education on adherence to TKI therapy and close monitoring of patient's adherence is critical to achieve optimal responses.[168,169] In a significant proportion of patients with TKI-induced toxicities, responses have been observed with doses well below their determined maximal tolerated doses.[170] Short interruptions or dose reductions, when medically necessary, may not have a negative impact on the control of disease or other outcomes. Adequate and appropriate management of side effects and scheduling appropriate follow-ups to review side effects could be helpful to improve patient adherence to therapy.

Disease Progression on TKI Therapy

Disease progression is defined as loss of hematologic or cytogenetic response or progression to accelerated phase or blast phase (lymphoid or myeloid). The panel recommends bone marrow cytogenetics and mutational analysis prior to initiation of treatment. Participation in a clinical trial is recommended for all patients with disease progression.

Accelerated Phase

No uniform consensus was reached about the definition of accelerated phase CML; therefore, 4 different definitions are provided in the guidelines.[171-174] See "Definitions for Accelerated Phase" in the guidelines. It should be noted that clinical trials of TKIs have largely reported efficacy data using the M.D. Anderson Cancer Center disease phase criteria.

Dasatinib or nilotinib are appropriate options for patients with disease progression to accelerated phase following TKI therapy. Allogeneic HSCT can be considered based on response to TKI therapy.

Blast Phase

According to the International Bone Marrow Transplant Registry (IBMTR), blast crisis is defined as 30% or greater blasts in the blood, bone marrow, or both, or as the presence of extramedullary disease.[175] In the World Health Organization (WHO) criteria, blast crisis is defined as 20% or greater blast cells in the peripheral blood or bone marrow, the presence of extramedullary blast proliferation and large foci or clusters of blasts in the bone marrow biopsy.[174] See "Definitions for Blast Phase" in the guidelines.

TKI followed by allogeneic HSCT, if feasible, is recommended for patients in myeloid or lymphoid blast phase. The addition of TKI to chemotherapy has been shown to improve outcome in patients with de

novo or minimally treated or newly diagnosed Ph-positive ALL.[176,177-180] Chemotherapy with TKI (ALL-type induction therapy for those with a lymphoid blast crisis and AML-type induction therapy for those with a myeloid blast crisis) followed by allogeneic HSCT, if feasible can be considered. Selection of TKI is based on prior therapy and/or mutation testing.

Allogeneic Hematopoietic Stem Cell Transplant

Allogeneic HSCT is a potentially curative treatment for patients with CML but the excellent results with imatinib have challenged the role of allogeneic transplant as a first line therapy.[181]The widespread application of allogeneic HSCT is limited by donor availability and the high toxicity of the procedure in older patients, which limits the age of eligibility at many centers to younger than 65 years.

Ongoing advances in alternative donor sources (such as unrelated donors and cord blood), more accurate human leukocyte antigen (HLA) typing of unrelated donors, and less toxic regimens are broadening the use of HSCT. Transplants from unrelated matched donors can now be used for many patients with CML. The advent of molecular DNA assessment of HLA typing has enabled a rigorous and stringent selection of unrelated matched donors, and this improvement in typing has translated into greatly improved transplant outcomes, so that results with unrelated, fully matched donors are comparable to those of matched-related donors.[182, 183,184]

The potential use of transplantation must be tied to faithful monitoring of disease, since the major potential pitfall in delaying transplantation is “missing” the chronic phase interval. Outcome is clearly better for patients in chronic phase who receive transplants when compared to patients with advanced disease; 5-year survival rates after matched-related transplants are approximately 75%, 40%, and 10% for patients in chronic, accelerated, and blast crisis phases, respectively.[184]

The German CML Study IV recently reported their results on 84 patients who underwent allogeneic HSCT because of either a high-disease risk score at diagnosis, imatinib failure, or disease progression.[185] The three-year survival rates were 91% for patients with chronic phase cases and 59% for those with advanced phase. Treatment-related mortality was 8%. A recent report from the M.D. Andersen Cancer Center indicated that allogeneic HSCT is an effective strategy for patients with CML who have the T315I mutation, particularly in earlier stages.[186] These findings indicate that allogeneic HSCT is an appropriate treatment option for patients who have failed TKI therapy and for those with T315I mutations.

Investigational approaches using non-myeloablative “mini transplants” have been pioneered to engender a graft-versus-leukemia effect without exposing the patient to the toxicity associated with the myeloablative preparative regimen.[187-192] These studies are still investigational but are quite promising and show that molecular remissions may be achieved in patients with CML.

There has been concern that previous treatment with imatinib might have a deleterious effect on subsequent transplant outcomes, as previously implicated with busulfan and interferon.[193-195] However, several large studies that have examined the use of imatinib prior to transplant have found no significant increase in death, relapse rate and non-relapse mortality compared to cases who did not receive pre-transplant imatinib.[196-199] These data suggest that pre-transplant imatinib does not compromise the outcome of a subsequent allogeneic transplant. In fact IBMTR data showed prior use of imatinib to be associated with improved survival for patients transplanted in chronic

phase.[198] Some studies have also shown that the use of second generation TKI before allogeneic HSCT does not affect the outcome of transplant nor increases transplant-related toxicity.[200-203]

NCCN recommendations

Chronic phase CML

NCCN recommendations have changed since the 5-year follow-up data of IRIS trial showed excellent survival benefit for imatinib. Allogeneic HSCT is no longer recommended as a first-line treatment for chronic phase CML.[204] Role of HSCT in the treatment of CML should be discussed with the patient. Allogeneic HSCT is recommended for patients with T315I mutation who do not respond to imatinib, dasatinib or nilotinib. Nonmyeloablative transplant is investigational and it should be performed only in the context of a clinical trial.

Evaluation of the patient for allogeneic HSCT is recommended for all patients with inadequate response (as listed below) to standard dose imatinib:

- Less than CHR at 3 months
- No cytogenetic response at 6 months
- Minor or no cytogenetic response at 12-months
- Partial cytogenetic response at 18 months
- Cytogenetic relapse at 12 or 18 months

Disease Progression

Allogeneic HSCT can be considered for patients with disease progression after first-line TKI therapy. In patients with disease progression on TKI therapy, treatment with a course of alternate TKI (not received before) will be beneficial as a “bridge” to transplantation.

Disease Monitoring after allogeneic HSCT

The *BCR-ABL* transcripts persist after many years in most patients after allogeneic HSCT. Several studies have examined the clinical significance of monitoring *BCR-ABL* transcript levels by QPCR following HSCT.[205-210] Radich et al reported that PCR-positivity 6 or 12 months after HSCT is associated with a higher risk of disease relapse (42%) compared to only 3% in patients who tested PCR-negative. This study also showed that early PCR-positivity is associated with more aggressive disease and high risk of relapse.[207] Olavarria et al reported similar findings. QPCR was performed at 3-5 months after allogeneic HSCT. At 3 years after allogeneic HSCT, the cumulative relapse rate was 17% for patients with no evidence of *BCR-ABL* transcripts, 43% for those who had less than 100 *BCR-ABL* transcripts and 86% for those with more than 100 *BCR-ABL* transcripts. [209] PCR-positivity at 6 months or less was also highly predictive of relapse in patients who received T-cell depleted transplant.[208] The prognostic significance of *BCR-ABL* positivity is less evident after a longer period of time following transplantation. Costello et al reported that the relapse rate was only 8% in patients who were *BCR-ABL* positive at more than 36 months after HSCT.[211] Other investigators have reported that *BCR-ABL* transcripts persist even in patients who are in complete remission for more than 10 years after HSCT.[212] More recently, Radich et al analyzed 379 consecutive CML patients alive at 18 months or more after HSCT to assess the relapse risk associated with *BCR-ABL* detection in "late" CML survivors.[210] Ninety of 379 patients (24%) had at least one positive *BCR-ABL* test 18 months after transplantation or later; 13 of 90 *BCR-ABL*-positive patients (14%) and 3 of 289 *BCR-ABL*-negative patients (1.0%) relapsed.

Thus, the prognostic significance of *BCR-ABL* positivity is influenced by the time of testing after transplantation. While QPCR assay positive for

BCR-ABL at 6 to 12 months after transplant is associated with a high risk of relapse, a positive QPCR assay at a much later time point after transplant is associated with a lower risk of relapse. Early detection of *BCR-ABL* transcripts after transplant may be useful to identify patients who may be in need of alternative therapies before the onset of a complete relapse.

Follow-up therapy

Donor lymphocyte infusion (DLI) is effective in inducing remissions in patients with relapsed CML following allogeneic HSCT, though it is more effective in chronic phase than advanced phase.[213] DLI induces complete remissions in majority of patients with CML in early-stage relapse.[214] DLI is also associated with complications such as graft-vs-host disease (GVHD), susceptibility to infections and immunosuppression. Improvements in the methods of detecting *BCR-ABL* transcripts to predict relapse, modified delivery of lymphocytes with the deletion of CD8+ cells and escalating the dose of donor T-cells and the development of reduced intensity conditioning regimens have reduced the incidence of GVHD.[215, 216]

Recently imatinib has been shown to be very effective in inducing remissions, particularly in patients with relapsed chronic phase CML following allogeneic HSCT.[199, 217-220] However, in a recent retrospective analysis, disease-free survival was significantly higher for patients receiving DLI than for those in the imatinib group.[221] There was also a trend towards higher rates of complete molecular remissions in the DLI group. These observations are yet to be confirmed in randomized trials. In patients who have previously failed imatinib, there are no data to support the use of post transplant imatinib. Other TKIs like dasatinib or nilotinib may be more appropriate. For patients who undergo allogeneic HSCT for blast phase in first remission, it is reasonable to employ imatinib or dasatinib as maintenance therapy post-transplant. Dasatinib has been shown to eradicate CNS leukemia.[222]

NCCN Recommendations

Patients who continue to be in complete cytogenetic remission (QPCR-negative) should undergo regular QPCR monitoring (every 3 months for 2 years, then 6 months for 3 years). Imatinib, dasatinib, DLI or interferon or PEG- interferon can be considered as options for patients who are in cytogenetic relapse. Discussion of treatment options with a transplant team is recommended. Participation in a clinical trial should be considered. For patients who are not in remission or in cytogenetic relapse after allogeneic HSCT, monitored withdrawal of immune suppression is recommended prior to the initiation of follow-up therapy with imatinib, dasatinib, DLI, or interferon or PEG-interferon.

Summary

CML is a hematopoietic stem cell disease which is characterized by the presence of Philadelphia chromosome (Ph-chromosome) resulting from the translocation between chromosomes 9 and 22 [t(9;22].

The development of imatinib mesylate, a potent and specific inhibitor of the BCR-ABL tyrosine kinase has revolutionized the treatment of CML. The results of the IRIS trial established the safety, efficacy and excellent survival benefit for imatinib in patients with newly diagnosed CML. Imatinib mesylate is the standard first-line treatment for newly diagnosed chronic phase CML, at an initial standard dose of 400 mg daily. In recent randomized studies, dasatinib and nilotinib were associated with significantly higher response rates and reduction in the 12-month incidence of accelerated or blast phase in newly diagnosed patients with CML. The guidelines have now included dasatinib and

nilotinib as alternative treatment options for patients with newly diagnosed CML.

Monitoring treatment response to TKI therapy is crucial in the management of patients with CML to assess response and detect resistance. NCCN guidelines recommend monitoring response at 3, 6, 12 and 18 months. Mutational status at the time of loss of response to first generation TKI would be helpful in the selection of subsequent TKI therapy. NCCN guidelines recommend mutational analysis if there is inadequate initial response, any sign of loss of response or disease progression.

Primary hematologic resistance to imatinib is very rare in patients with newly diagnosed CML, whereas primary cytogenetic resistance is observed in 15-25% of patients. Additionally, some patients will eventually develop secondary resistance to imatinib related to the presence of *BCR-ABL* mutations resulting in disease progression. Dose escalation of imatinib has been shown to overcome resistance in some patients with cytogenetic failure on standard dose imatinib, particularly those with prior cytogenetic response. Dasatinib and nilotinib are effective in patients with imatinib resistant or intolerant CML. Patients not responding to a second-generation TKI in the first-line setting should be switched to the other second-generation TKI (that they have not received before) for second-line therapy.

Dasatinib or nilotinib are recommended for those who progress to accelerated phase. Allogeneic HSCT can be considered based on response to therapy. TKI therapy either alone or in combination with chemotherapy followed by allogeneic HSCT is recommended for patients progressing to blast phase.

Allogeneic HSCT remains a potentially curative treatment for patients with CML and is recommended for patients with T315I mutation as well as for those who progress to accelerated or blast phase. For most patients, a trial of alternate TKI (not received before) is reasonable before proceeding to allogeneic HSCT.

Availability of more potent TKIs has widened the treatment options and the outlook for patients with CML continues to look promising. Selection of appropriate TKI therapy will depend on the stage of the disease, the agent's side effect profile and its relative effectiveness against *BCR-ABL* mutations

		IC_{50} fold increase (WT = 1)			
		Bosutinib	Imatinib	Dasatinib	Nilotinib
	Parental	38.31	10.78	> 50	38.43
	WT	1	1	1	1
P-LOOP	L248V	2.97	3.54	5.11	2.80
	G250E	4.31	6.86	4.45	4.56
	Q252H	0.81	1.39	3.05	2.64
	Y253F	0.96	3.58	1.58	3.23
	E255K	9.47	6.02	5.61	6.69
	E255V	5.53	16.99	3.44	10.31
C-Helix	D276G	0.60	2.18	1.44	2.00
	E279K	0.95	3.55	1.64	2.05
ATP binding region (drug contact sites)	V299L	26.10	1.54	8.65	1.34
	T315I	45.42	17.50	75.03	39.41
	F317L	2.42	2.60	4.46	2.22
SH2-contact	M351T	0.70	1.76	0.88	0.44
Substrate binding region (drug contact sites)	F359V	0.93	2.86	1.49	5.16
A-LOOP	L384M	0.47	1.28	2.21	2.33
	H396P	0.43	2.43	1.07	2.41
	H396R	0.81	3.91	1.63	3.10
	G398R	1.16	0.35	0.69	0.49
C terminal lobe	F486S	2.31	8.10	3.04	1.85

Sensitive	≤ 2
Moderately resistant	2.01-4
Resistant	4.01-10
Highly resistant	> 10

Fig 1. IC_{50} values for bosutinib, imatinib, dasatinib, and nilotinib against 18 mutated forms of BCR/ABL expressed in Ba/F3 transfected cells. IC_{50}, relative concentration that inhibits 50%; WT, wild type; P loop, phosphate-binding loop; ATP, adenosine triphosphate; SH2, Src homology 2; A loop, activation loop. Reprinted with permission. © 2008 American Society of Clinical Oncology. All Rights Reserved. Redaelli S, Piazza R, Rostagno R, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib resistant BCR/ABL mutants. J Clin Oncol. Vol. 27(3), 2009:469-471.

Table 1. Calculation of Relative Risk

Study	Calculation	Risk Definition by Calculation	
Sokal et al, 1984[6]	Exp 0.0116 × (age in years − 43.4) + 0.0345 × (spleen − 7.51) + 0.188 × [(platelet count ÷ 700)2 − 0.563] + 0.0887 × (blast cells − 2.10)	Low Intermediate High	< 0.8 0.8 – 1.2 > 1.2
Hasford et al, 1998[7]	0.666 when age ≥ 50 years + (0.042 × spleen) + 1.0956 when platelet count > 1,500 × 109L + (0.0584 × blast cells) + 0.20399 when basophils > 3% + (0.0413 × eosinophils) × 100	Low Intermediate High	≤ 780 781-1,480 > 1,480

NOTE. Calculation of relative risk found at 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.

Table 2. Recommendations for Monitoring Response to TKI Therapy and Mutational Analysis

Test	Indication
Bone Marrow Cytogenetics	• At diagnosis to establish the stage. If collection of bone marrow is not feasible, FISH on a peripheral blood specimen using dual probes for the *BCR* and *ABL* genes is an acceptable method of confirming the diagnosis of CML. • At 6, 12 and 18 months from initiation of therapy to assess response to TKI therapy. If a CCyR is achieved at either of the earlier time points, then cytogenetics do not need to be repeated. • Rising levels of *BCR-ABL* transcript (1 log increase) without a MMR.
Quantitative RT-PCR (QPCR)	• At diagnosis to establish baseline *BCR-ABL* transcript level. • Every 3 months when a patient is responding to treatment and every 3-6 months after CCyR. • If there is a rising levels of *BCR-ABL* transcript (1 log increase) with a MMR, QPCR analysis should be repeated in 1-3 months.
ABL tyrosine kinase domain mutation analysis	• If there is inadequate initial response (failure to achieve CHR at 3 months, minimal cytogenetic response at 6 months or MCyR at 12 months), any sign of loss of response (defined as hematologic or cytogenetic relapse or 1 log increase in *BCR-ABL* transcript levels and loss of MMR). • Disease progression to accelerated or blast phase.

Table 3. Recommendations for Follow-up Therapy

Response	Recommendation
• Complete hematologic response at 3 months • Complete or partial cytogenetic response at 6 months • Complete cytogenetic response at 12 and 18 months	• Continue same dose of imatinib, dasatinib or nilotinib.
• Minor cytogenetic response at 6 months • Partial cytogenetic response at 12 months	• Continue same dose of imatinib, dasatinib or nilotinib OR increase the dose of imatinib to a maximum of 800 mg, as tolerated.
• Less than complete hematologic response at 3 months • No cytogenetic response at 6 months • Minor or no cytogenetic response at 12 months • Partial cytogenetic response or cytogenetic relapse at 18 months	• Evaluate patient compliance and drug interactions • Consider mutational analysis • Switch to dasatinib or nilotinib (if prior therapy is imatinib); nilotinib (if prior therapy is dasatinib) or dasatinib (if prior therapy is nilotinib) • Evaluate for allogeneic HSCT depending on response to TKI therapy • Consider participation in clinical trials
• Cytogenetic relapse at 12 months	• Evaluate patient compliance and drug interactions • Consider mutational analysis • Switch to dasatinib or nilotinib (if prior therapy is imatinib); nilotinib (if prior therapy is dasatinib) or dasatinib (if prior therapy is nilotinib) OR increase the dose of imatinib to a maximum of 800 mg, as tolerated. • Evaluate for allogeneic HSCT depending on response to TKI therapy • Consider participation in clinical trials

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