



NCCN Clinical Practice Guidelines in Oncology™

Chronic Myelogenous Leukemia

V.1.2009

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[NCCN Guidelines Panel Disclosures](#)

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This manuscript is being updated to correspond with the newly updated algorithm.

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](#)

These guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations or warranties of any kind, regarding their content use or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2008.

Summary of the Guidelines updates

Summary of the changes in the 1.2009 version of the Chronic Myelogenous Leukemia guidelines from the 3.2008 version include:

CML-1

- Consider HLA typing was added to the workup recommendations.
- Footnote “b” is new to the page, “Bone marrow is preferable for the initial workup, not only to provide morphologic review, but to also detect chromosomal abnormalities that are not detectable on peripheral blood FISH.”
- Nilotinib was added to the other TKIs listed where if there is intolerability, patients may be considered for IFN or a clinical trial.

CML-2

- This page was reformatted to only include the recommendations for therapy after the 3 month evaluation.
- For patients not in hematologic remission, or in hematologic relapse, an interim evaluation was added to evaluate patient compliance and consider mutational analysis.
- The recommendation for HSCT was changed to include evaluation and discussion of HSCT.

CML-3

- This page was reformatted to only include the recommendations for therapy after the 6 month evaluation.
- For patients without a cytogenetic response, an interim evaluation was added to evaluate patient compliance and consider mutational analysis. The recommendation to increase imatinib was removed for this category.

CML-4

- This page was reformatted to only include the recommendations for therapy after the 12 month evaluation.
- For patients with a minor or no cytogenetic response or cytogenetic relapse, an interim evaluation was added to evaluate patient compliance and consider mutational analysis.

CML-5

- This page was reformatted to only include the recommendations for therapy after the 18 month evaluation.
- The category of “partial cytogenetic response” was separated out from “minor or no cytogenetic response”.
- For patients with a minor or no cytogenetic response or cytogenetic relapse, an interim evaluation was added to evaluate patient compliance and consider mutational analysis. The recommendation to increase imatinib was removed for this category.

CML-6

- The algorithm was modified and the delineation of GVHD was removed from “Not in remission, or in relapse”.
- The recommendation for “marrow cytogenetics” for positive PCR on follow-up after a complete remission was removed and treatment options listed.

CML-7

- Dasatinib was added to induction chemotherapy for patients with blast crisis.

CML-A

- For patients responding to treatment, the recommendation was added that a bone marrow is not necessary at 12 mo, if the patient has a CCyR at 6 mo.
- Patients with a CCyR, bone marrow cytogenetics are recommended as clinically indicated.
- Patients with a rising level of BCR-ABL transcripts, the recommendation to evaluate patient compliance was added. A 1 log increase with a MMR, the recommendation was changed to repeat in 1-3 mo. A 1 log increase without a MMR, the recommendation is to obtain bone marrow cytogenetics.

CML-C 1 of 3

- Nonhematologic toxicity- Grade 3-4 was separated out and the recommendation added to consider a change to dasatinib, nilotinib or a clinical trial.

CML-C 2 of 3

- Grapefruit juice was added due to the potential to increase plasma concentrations of imatinib.

CML-D 2 of 2

- Grapefruit juice was added due to the potential to increase plasma concentrations of dasatinib.

CML-E 2 of 2

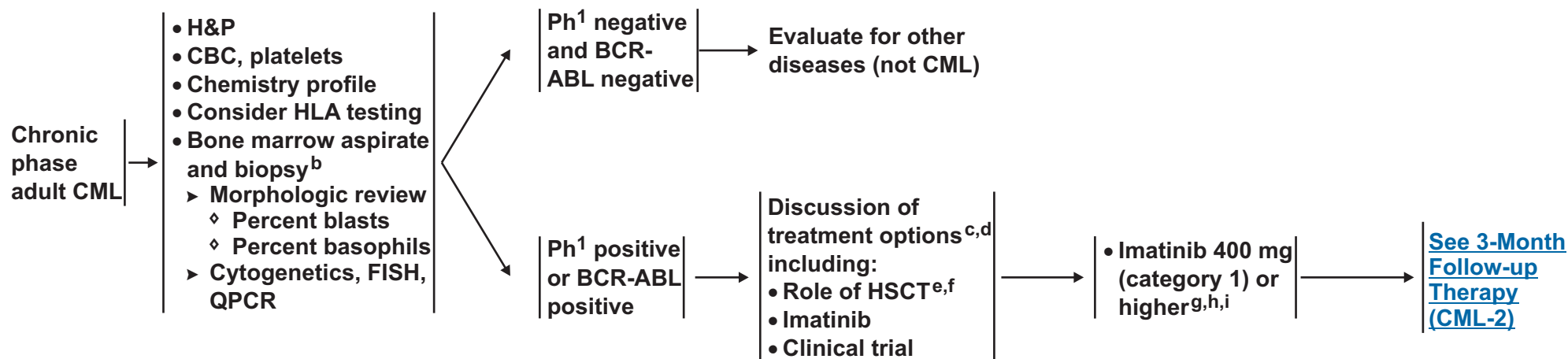
- Grapefruit juice was added due to the potential to increase plasma concentrations of nilotinib.

CML-F

- Major cytogenetic response and molecular responses were added.

WORKUP^a

PRIMARY TREATMENT



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

^bBone 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.

^cThere is 5 year follow-up data which shows clear evidence of excellent survival benefit with imatinib. See text for additional information.

^dFor patients with symptomatic leukocytosis or thrombocytosis, [see Supportive Care Strategies \(CML-B\).](#)

^eHSCT = hematopoietic stem cell transplantation. Refers to a matched related and unrelated allogeneic transplant. HLA testing should be performed if considering HSCT.

^fIndications 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.

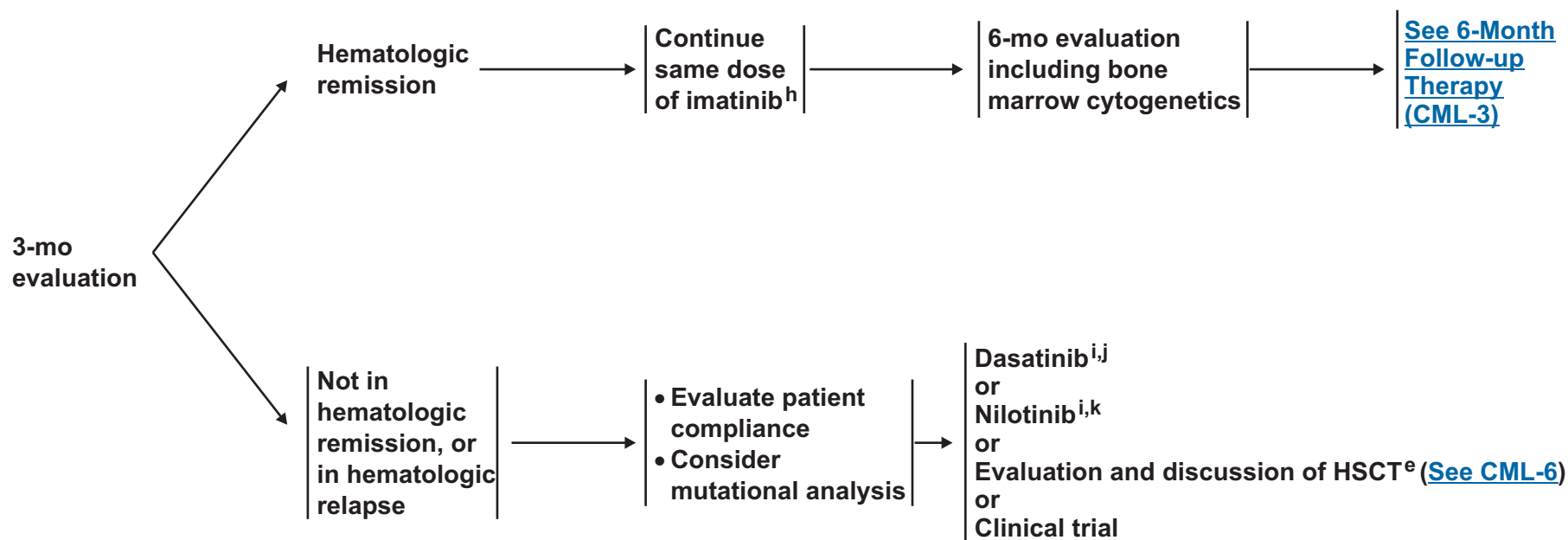
^gThere are some data suggesting increased efficacy with a higher dose of imatinib but this has not yet been demonstrated through randomized trials. Kantarjian H, Talpaz M, Garcia-Manero G, et al. High-dose imatinib mesylate therapy in newly diagnosed Philadelphia chromosome-positive chronic phase chronic myeloid leukemia. *Blood* 2004;103(8):2873-2878.

^h[See Management of Imatinib Toxicity \(CML-C\).](#)

ⁱRare patients unable to tolerate imatinib, dasatinib, or nilotinib then consider IFN or clinical trial.

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.

3 MONTH FOLLOW-UP THERAPY^a

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

^eHSCT = hematopoietic stem cell transplantation. Refers to a matched related and unrelated allogeneic transplant. HLA testing should be performed if considering HSCT.

^h[See Management of Imatinib Toxicity \(CML-C\).](#)

ⁱRare patients unable to tolerate imatinib, dasatinib, or nilotinib then consider IFN or clinical trial.

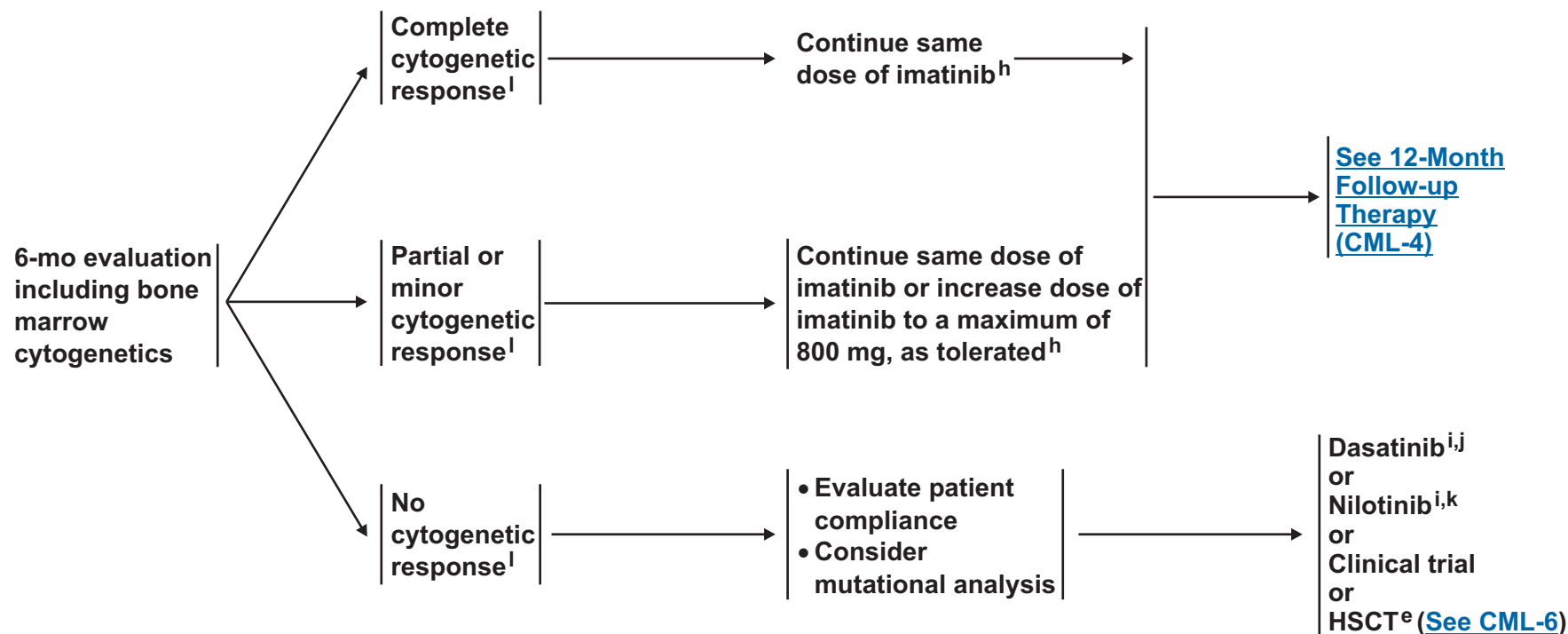
^j[See Management of Dasatinib Toxicity \(CML-D\).](#)

^k[See Management of Nilotinib Toxicity \(CML-E\).](#)

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6 MONTH FOLLOW-UP THERAPY^a



^aSee [Monitoring for Patients Receiving Tyrosine Kinase Inhibitor therapy \(CML-A\)](#).

^eHSCT = hematopoietic stem cell transplantation. Refers to a matched related and unrelated allogeneic transplant. HLA testing should be performed if considering HSCT.

^hSee [Management of Imatinib Toxicity \(CML-C\)](#).

ⁱRare patients unable to tolerate imatinib, dasatinib, or nilotinib then consider IFN or clinical trial.

^jSee [Management of Dasatinib Toxicity \(CML-D\)](#).

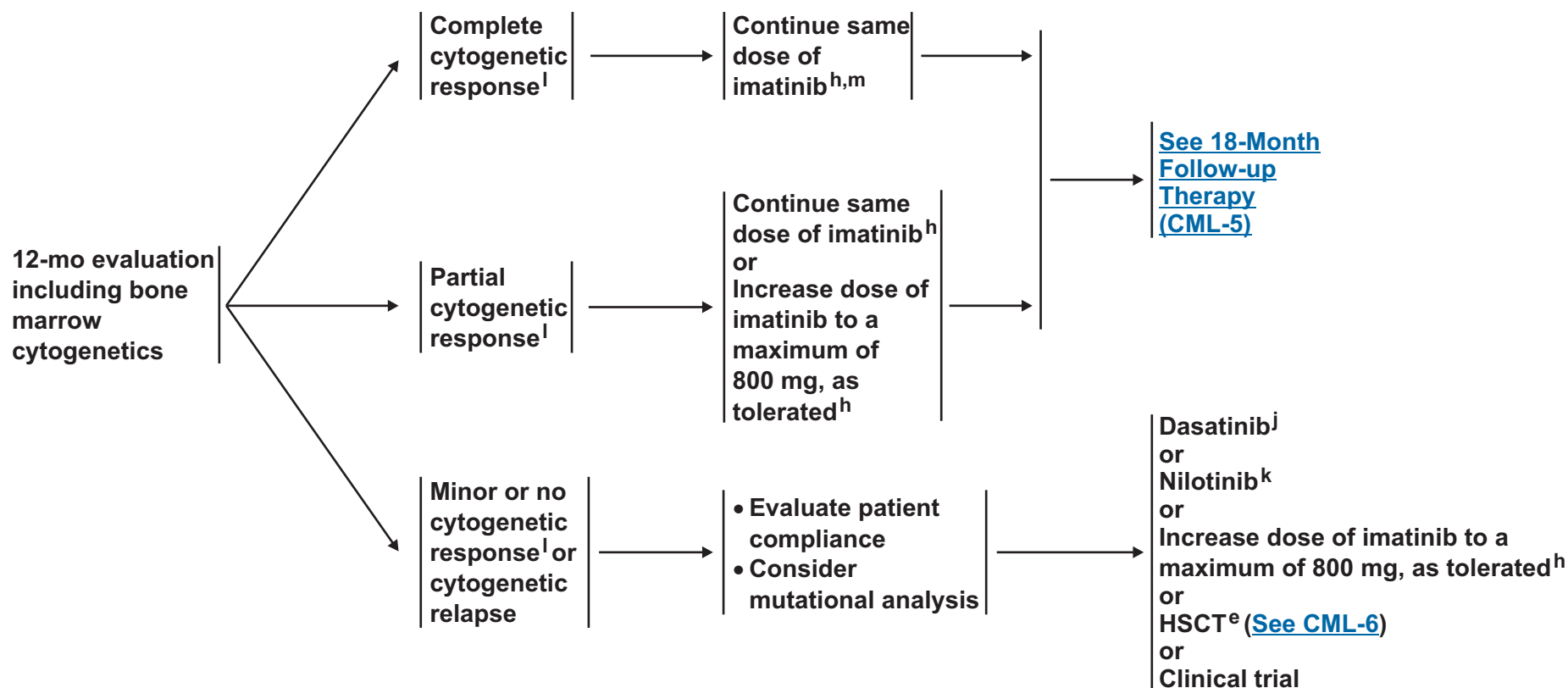
^kSee [Management of Nilotinib Toxicity \(CML-E\)](#).

^lSee [Criteria for Cytogenetic, Hematologic and Molecular Response \(CML-F\)](#).

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12 MONTH FOLLOW-UP THERAPY^a



^aSee [Monitoring for Patients Receiving Tyrosine Kinase Inhibitor therapy \(CML-A\)](#).

^eHSCT = hematopoietic stem cell transplantation. Refers to a matched related and unrelated allogeneic transplant. HLA testing should be performed if considering HSCT.

^hSee [Management of Imatinib Toxicity \(CML-C\)](#).

^jSee [Management of Dasatinib Toxicity \(CML-D\)](#).

^kSee [Management of Nilotinib Toxicity \(CML-E\)](#).

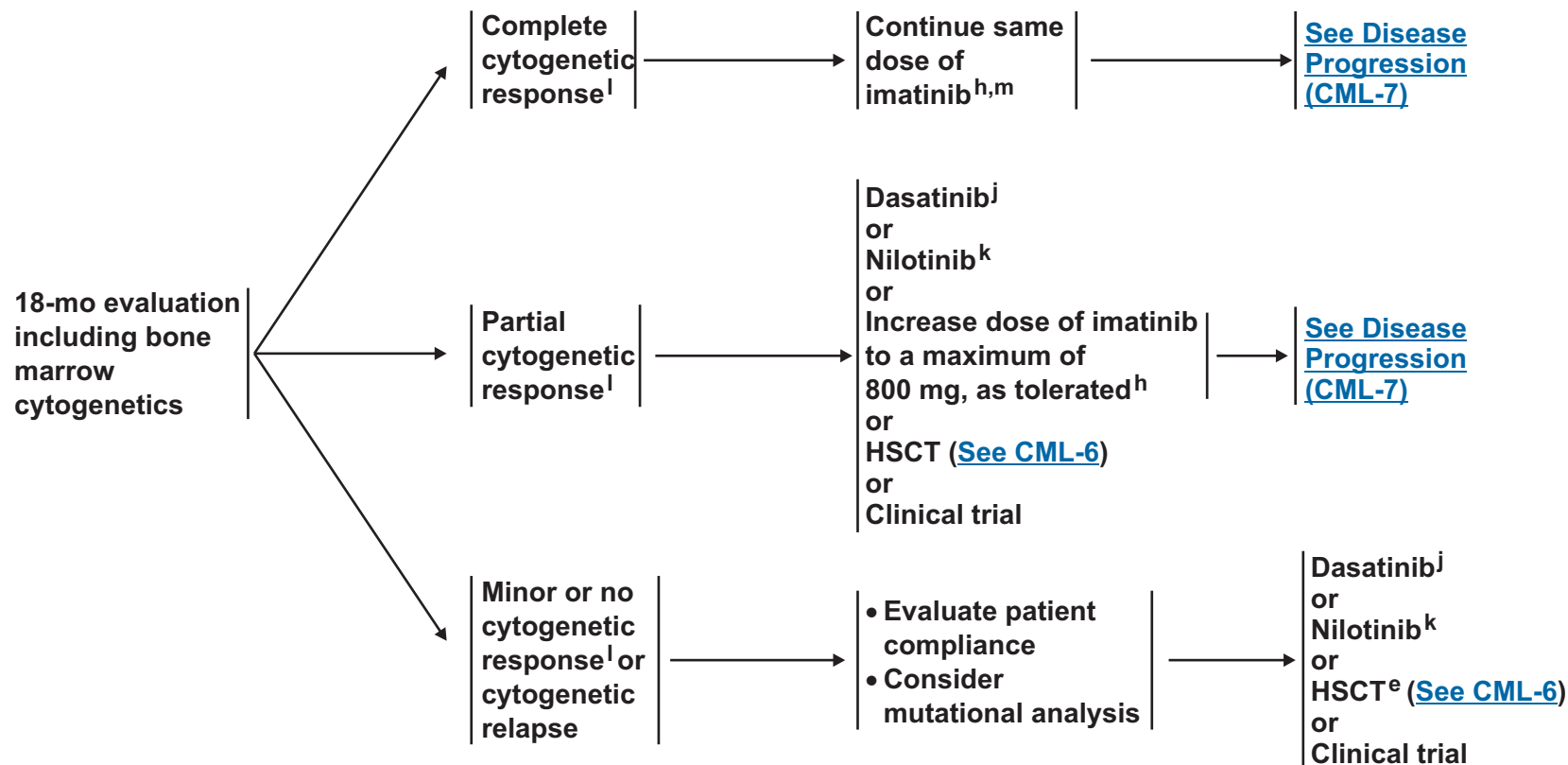
^lSee [Criteria for Cytogenetic, Hematologic and Molecular Response \(CML-F\)](#).

^mTherapy should continue indefinitely and not be discontinued.

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18 MONTH FOLLOW-UP THERAPY^a



^aSee [Monitoring for Patients Receiving Tyrosine Kinase Inhibitor therapy \(CML-A\)](#).

^eHSCT = hematopoietic stem cell transplantation. Refers to a matched related and unrelated allogeneic transplant. HLA testing should be performed if considering HSCT.

^hSee [Management of Imatinib Toxicity \(CML-C\)](#).

^jSee [Management of Dasatinib Toxicity \(CML-D\)](#).

^kSee [Management of Nilotinib Toxicity \(CML-E\)](#).

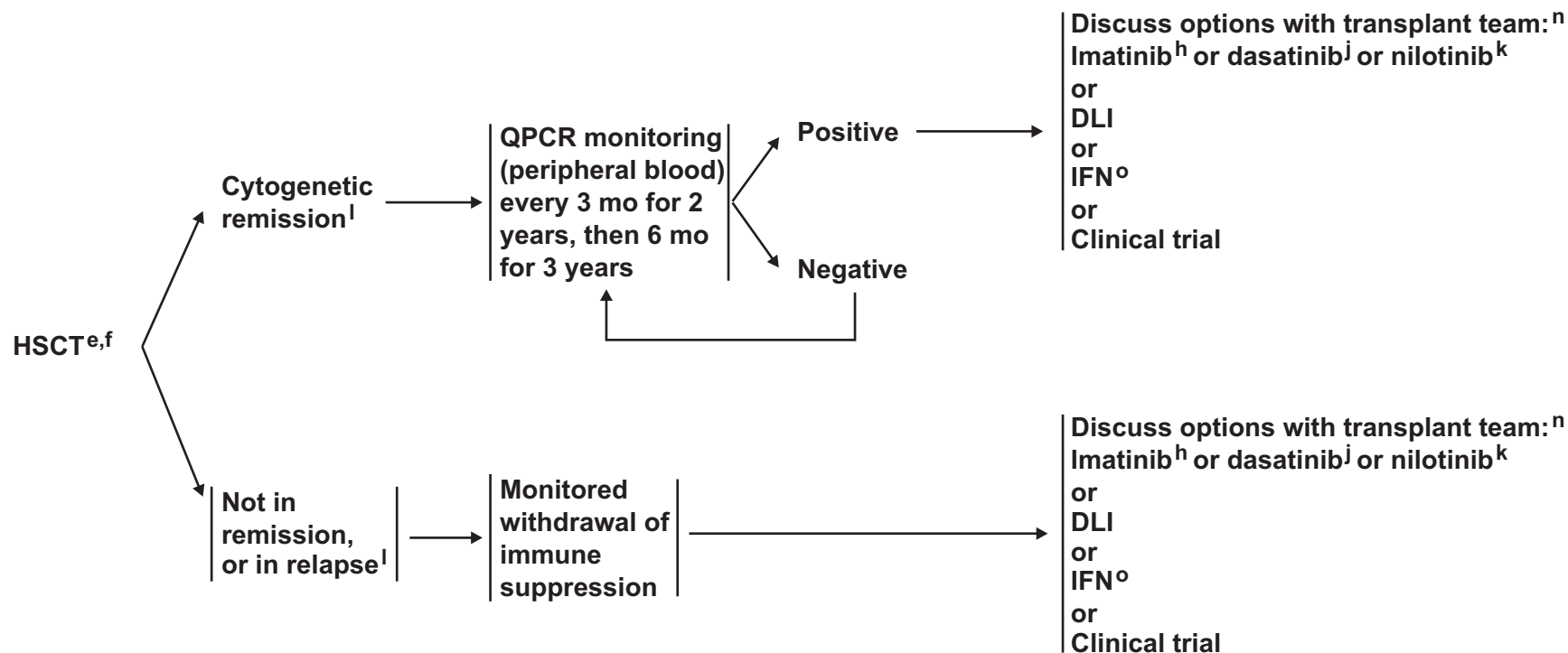
^lSee [Criteria for Cytogenetic, Hematologic and Molecular Response \(CML-F\)](#).

^mTherapy should continue indefinitely and not be discontinued.

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FOLLOW-UP THERAPY



^eHSCT = hematopoietic stem cell transplantation. Refers to a matched related and unrelated allogeneic transplant. HLA testing should be performed if considering HSCT.

^fIndications 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[See Management of Imatinib Toxicity \(CML-C\).](#)

^j[See Management of Dasatinib Toxicity \(CML-D\).](#)

^k[See Management of Nilotinib Toxicity \(CML-E\).](#)

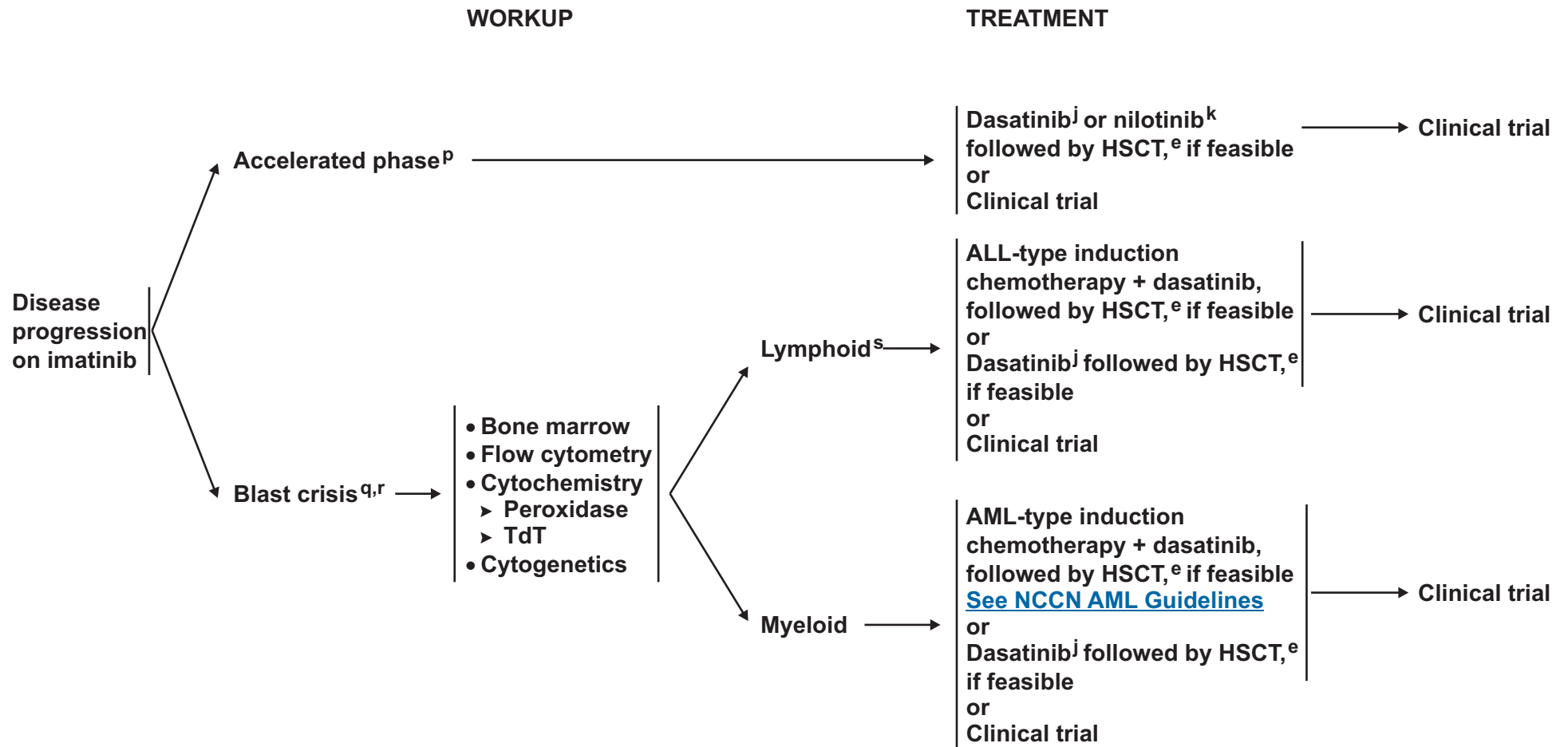
^l[See Criteria for Cytogenetic, Hematologic and Molecular Response \(CML-F\).](#)

ⁿThere 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.

^o[See Management of IFN Toxicity \(CML-G\).](#)

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^eHSCT = hematopoietic stem cell transplantation. Refers to a matched related and unrelated allogeneic transplant. HLA testing should be performed if considering HSCT.

^jSee [Management of Dasatinib Toxicity \(CML-D\)](#).

^kSee [Management of Nilotinib Toxicity \(CML-E\)](#).

^pSee [Definitions of Accelerated Phase \(CML-H\)](#).

^qSee [Definitions of Blast Crisis \(CML-I\)](#).

^rPatients 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.

^sConsider CNS prophylaxis/treatment.

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MONITORING FOR PATIENTS RECEIVING TYROSINE KINASE INHIBITOR THERAPY¹**Indications for cytogenetics and QPCR for BCR-ABL mRNA****At 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.

While a patient appears to be responding to treatment

- 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.

When a patient reaches CCyR

- BCR-ABL transcript levels should be measured every 3-6 months.
- Bone marrow cytogenetics as clinically indicated.

When a patient appears to have 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 may be considered**Chronic phase CML**

- ABL KD mutation screening may provide additional information 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, relapse to Ph-positivity or an increase in BCR-ABL transcript ratio, 1 log increase and loss of MMR).

Accelerated and blast phase CML

- Testing for KD mutations may provide additional information.

¹Hughes 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 (PAGE 1 of 3)¹**Hematologic³**

- Grade 3-4 neutropenia [absolute neutrophil count (ANC) < 1000/mm³]: Hold drug until ANC ≥ 1500/mm³, resume at the same dose if recovery occurs within 2 wks or at 25-33% dose reduction (not less than 300 mg) if ANC is < 1000/mm³ for more than 2 weeks.⁴
- Grade 3-4 thrombocytopenia (platelet count < 50,000/mm³): Hold drug until platelet count ≥ 75,000/mm³, resume at the same dose if recovery occurs within 2 wks or at 25-33% dose reduction (not less than 300 mg) if platelet counts < 50,000/mm³ for more than 2 wks.³
- In accelerated phase and blast phase, patients may have cytopenias related to disease. If cytopenia is unrelated to disease, reduce dose to 400 mg or 300 mg if cytopenia persists for 2 weeks. If cytopenia persists for 4 weeks, stop imatinib until ANC ≥ 1000/mm³ and platelet count ≥ 20,000/mm³, and then resume treatment at 300 mg.
- Growth factors can be used in combination with imatinib for patients with resistant neutropenia and thrombocytopenia.

Grade 3-4 anemia⁵**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 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 Information from FDA label, available at www.fda.gov.

² Many toxicities are self-limiting, consider re-escalating dose at a later time.

³ If patient remains nonresponsive with erythroid or myeloid therapy, consider obtaining bone marrow.

⁴ Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med 2002;346:645-652.

⁵ 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.

[Potential Drug Interactions \(see CML-C 2 of 3\)](#)

Note: All recommendations are category 2A unless otherwise indicated.

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POTENTIAL DRUG INTERACTIONS WITH IMATINIB (2 of 3)⁶

DRUG	INTERACTION
acetaminophen	Imatinib can cause LFT abnormalities. Liver failure and death occurred in one patient taking large doses of both acetaminophen and imatinib. The use of acetaminophen should be limited in patients taking imatinib. For most patients, this means taking 1300 mg acetaminophen/day or less.
aprepitant	Aprepitant inhibits CYP450 3A4, increasing the imatinib plasma concentration.
carbamazepine	Carbamazepine induces CYP450 3A4 and decreases the plasma concentration of imatinib. Increase in imatinib dose is usually necessary.
clarithromycin	Clarithromycin inhibits CYP450 3A4, increasing the imatinib plasma concentration
cyclosporine	Imatinib inhibits CYP450 3A4, increasing the cyclosporine plasma concentration; this is a concern given the narrow therapeutic window of cyclosporine.
dexamethasone	Dexamethasone induces CYP450 3A4, decreasing the imatinib plasma concentration. Increase in imatinib dose is usually necessary.
erythromycin	Erythromycin inhibits CYP450 3A4, increasing the imatinib plasma concentration
grapefruit juice	Grapefruit juice may increase plasma concentrations of imatinib and should be avoided
hypericum perforatum	St. John's Wort induces CYP450 3A4 and may decrease the imatinib plasma concentration. Increase in imatinib dose may be necessary in patients receiving St. John's Wort.
itraconazole	Itraconazole inhibits CYP450 3A4, increasing the imatinib plasma concentration.

CYP450 = cytochrome P450; LFT = liver function test.

⁶Demetri GD, Benjamin R, Blanke CD, et al. NCCN Task Force Report : Optimal management of patients with gastrointestinal stromal tumor (GIST)--Update of NCCN Clinical Practice Guidelines. JNCCN 2007;5(suppl2):S1-S31.

[Potential Drug Interactions continued](#)
(see [CML-C 3 of 3](#))

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POTENTIAL DRUG INTERACTIONS WITH IMATINIB (3 of 3)⁶

DRUG	INTERACTION
ketoconazole	Ketoconazole inhibits CYP450 3A4, increasing the imatinib plasma concentration.
phenobarbital	Phenobarbital induces CYP450 3A4, decreasing the imatinib plasma concentration. Increase in imatinib dose is usually necessary.
phenytoin	Phenytoin induces CYP450 3A4, decreasing the imatinib plasma concentration. Increase in imatinib dose is usually necessary.
pimozide	Imatinib inhibits CYP450 3A4, increasing pimozide plasma concentration. This is a concern given the narrow therapeutic window of pimozide.
rifabutin	Rifabutin induces CYP450 3A4, decreasing the imatinib plasma concentration. Increase in imatinib dose is usually necessary.
rifampin	Rifampin induces CYP450 3A4, decreasing the imatinib plasma concentration. Increase in imatinib dose is usually necessary.
rifapentine	Rifapentine induces CYP450 3A4, decreasing the imatinib plasma concentration. Increase in imatinib dose is usually necessary.
simvastatin	Imatinib inhibits CYP450 3A4, increasing the simvastatin plasma concentration. A dose adjustment of simvastatin may be necessary.
warfarin	Warfarin is metabolized by the CYP450 isoenzymes CYP 2C9 and CYP 3A4. Use of warfarin with imatinib could cause an increase in the availability of warfarin. Patients requiring anticoagulation should be given heparin or low-molecular-weight heparin instead of warfarin.

CYP450 = cytochrome P450; LFT = liver function test.

⁶Demetri GD, Benjamin R, Blanke CD, et al. NCCN Task Force Report : Optimal management of patients with gastrointestinal stromal tumor (GIST)--Update of NCCN Clinical Practice Guidelines. JNCCN 2007;5(suppl2):S1-S31.

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MANAGEMENT OF DASATINIB TOXICITY¹ (1 of 2)**Hematologic²**

- Grade 3-4 neutropenia (absolute neutrophil count (ANC) < 500/mm³): Hold drug until ANC ≥ 1000/mm³, resume at original starting dose if recovery occurs within 7 days or reduce one dose level if ANC < 500/mm³ for more than 7 days.
- Grade 3-4 thrombocytopenia (platelet count < 50,000/mm³): Hold drug until platelet count ≥ 50,000/mm³, resume at original starting dose if recovery occurs within 7 days or reduce one dose level if platelet count < 25,000/mm³ for more than 7 days.
- In accelerated phase and blast phase, patients may have cytopenias related to disease. If cytopenia is unrelated to disease, hold drug until ANC ≥ 1000/mm³ and platelet count ≥ 20,000/mm³, resume at original starting dose or reduce one dose level if cytopenia persists. If cytopenia is related to leukemia, consider dose escalation to 100 mg twice daily.
- Growth factors can be used in combination with dasatinib for patients with resistant neutropenia and thrombocytopenia.

Grade 3-4 anemia³**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

Nonhematologic²

- Grade 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.

Dose Levels (chronic phase)

0	100 mg	Daily
-1	80 mg	Daily

Dose Levels (accelerated or blast phase)

0	70 mg	BID
-1	50 mg	BID
-2	40 mg	BID

¹Information from FDA label, available at www.fda.gov.

Potential Drug Interactions (see CML-D 2 of 2)

²Data suggest single dose dasatinib at 100 mg may decrease the side effects and efficacy may be comparable. Shah NP, Kantarjian HM, Kim, D et al. Intermittent target inhibition with dasatinib once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic phase chronic myeloid leukemia. J Clin Oncol 2008;26(19):3204-3212.

³Although 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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POTENTIAL DRUG INTERACTIONS WITH DASATINIB (2 of 2)¹**Drugs that may increase dasatinib plasma concentrations**

CYP3A4 Inhibitors: Dasatinib is a CYP3A4 substrate. Concomitant use of dasatinib and drugs that inhibit CYP3A4 (eg, ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, telithromycin) may increase exposure to dasatinib and should be avoided. In patients receiving treatment with dasatinib, close monitoring for toxicity and a dose reduction should be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.

Drugs that may decrease dasatinib plasma concentrations

CYP3A4 Inducers: Drugs that induce CYP3A4 activity may decrease dasatinib plasma concentrations. In patients in whom CYP3A4 inducers (eg, dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital) are indicated, alternative agents with less enzyme induction potential should be used. If dasatinib must be administered with a CYP3A4 inducer, a dose increase in dasatinib should be considered. St. John's wort (*Hypericum perforatum*) may decrease dasatinib plasma concentrations unpredictably. Patients receiving dasatinib should not take St. John's wort.

Antacids: Nonclinical data demonstrate that the solubility of dasatinib is pH dependent. Simultaneous administration of dasatinib with antacids should be avoided. If antacid therapy is needed, the antacid dose should be administered at least 2 hours prior to or 2 hours after the dose of dasatinib.

H2 Blockers/Proton Pump Inhibitors: Long-term suppression of gastric acid secretion by H2 blockers or proton pump inhibitors (eg, famotidine and omeprazole) is likely to reduce dasatinib exposure. The concomitant use of H2 blockers or proton pump inhibitors with dasatinib is not recommended. The use of antacids should be considered in place of H2 blockers or proton pump inhibitors in patients receiving dasatinib therapy.

Drugs that may have their plasma concentration altered by dasatinib

CYP3A4 Substrates: Dasatinib is a time-dependent inhibitor of CYP3A4. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozone, quinidine, sirolimus, tacrolimus, or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving dasatinib. Grapefruit juice may increase plasma concentrations of dasatinib and should be avoided.

¹Information from FDA label, available at www.fda.gov.

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.

MANAGEMENT OF NILOTINIB TOXICITY¹ (1 of 2)**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 (400 mg twice daily) 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 a day). 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. Patients should avoid food 2 hours before and 1 hour after taking each dose of nilotinib.

Hematologic

- Grade 3-4 neutropenia [absolute neutrophil count (ANC) < 1000/mm³]: Hold drug until ANC is ≥ 1000/mm³, resume at prior dose (400 mg twice daily) if recovery occurs within 2 weeks, or reduce the dose to 400 mg once daily, if ANC is < 1000/mm³ for more than 2 weeks.
- Grade 3-4 thrombocytopenia (platelet count < 50,000/mm³): Hold drug until the platelet count is ≥ 50,000/mm³, 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/mm³ for more than 2 weeks.
- Growth factors can be used in combination with nilotinib for patients with resistant neutropenia and thrombocytopenia.

- Grade 3-4 anemia²

Specific Interventions

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

Nonhematologic

- Grade 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 400 mg twice daily.

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.

¹Information from FDA label, available at www.fda.gov.

²Although 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.

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POTENTIAL DRUG INTERACTIONS WITH NILOTINIB¹ (2 of 2)**Drugs that may increase nilotinib plasma concentrations**

CYP3A4 Inhibitors: Nilotinib is a competitive inhibitor of CYP3A4. Concomitant administration of strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase systemic exposure to nilotinib and should be avoided. It is recommended that treatment with nilotinib should be interrupted, if patient requires systemic administration of a potent CYP3A4 inhibitor. If interruption of nilotinib is not possible, dose reduction should be considered and close monitoring for prolongation of QT interval is indicated. If the CYP3A4 inhibitor is discontinued, nilotinib dose should be increased after a washout period.

P-Glycoprotein (Pgp, ABCB1) Inhibitors: Nilotinib is a substrate of the efflux transporter P-glycoprotein (Pgp, ABCB1). If nilotinib is administered with drugs that inhibit Pgp, concentrations of nilotinib are likely to increase. Nilotinib should be used with caution when it is co administered with Pgp inhibitors.

Drugs that may decrease nilotinib plasma concentrations

CYP3A4 Inducers: Drugs that induce CYP3A4 activity may decrease nilotinib plasma concentrations. The concomitant use of strong CYP3A4 inducers (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital) should be avoided. Patients receiving nilotinib should not take St. John's wort. If nilotinib must be administered with a CYP3A4 inducer, a dose increase in nilotinib should be considered, depending on patient's tolerability. Nilotinib dose should be reduced to the indicated dose after the discontinuation of CYP3A4 inducers.

Drugs that may have their plasma concentration altered by nilotinib

Nilotinib is an inhibitor of human Pgp, CYP2C8, CYP2C9, CYP2D6 and UGT1A1, potentially increasing the concentrations of drugs eliminated by these enzymes. In addition, nilotinib may induce CYP2B6, CYP2C8 and CYP2C9, and thereby decreasing the concentrations of drugs which are eliminated by these enzymes. Therefore, drugs that are substrates for these enzymes that have a narrow therapeutic index should be administered with caution in patients receiving nilotinib. Grapefruit juice may increase plasma concentrations of nilotinib and should be avoided.

¹Information from FDA label, available at www.fda.gov.

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CRITERIA FOR CYTOGENETIC, HEMATOLOGIC AND MOLECULAR RESPONSE¹**Cytogenetic response²**

- Complete- No Ph¹-positive metaphases
- Major- 0%-35% Ph-positive metaphases (complete + partial)
- Partial- 1%-34% Ph-positive metaphases
- Minor- 35%-90% Ph-positive metaphases

Complete hematologic response

- Complete normalization of peripheral blood counts with leukocyte count < 10 x 10⁹/L
- Platelet count < 450 x 10⁹/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 10⁹/L
- Persistent splenomegaly, but < 50% of the pretreatment extent

Molecular response

- Complete molecular response - bcr-abl mRNA undetectable by RT-PCR
- Major molecular response ≥3-log reduction of bcr-abl mRNA

¹Adapted, 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.

²A 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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DEFINITIONS OF ACCELERATED PHASE

Criteria of Sokal et al ¹	International Bone Marrow Transplant Registry Criteria ²	Criteria Used at M.D. Anderson Cancer Center ³	World Health Organization (WHO) Criteria ⁴
<ul style="list-style-type: none"> • Peripheral blood or marrow blasts ≥ 5% • Basophils > 20% • Platelet count ≥ 1000 x 10⁹/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 	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Peripheral blood blasts ≥ 15% • Peripheral blood blasts and promyelocytes ≥ 30% • Peripheral blood basophils ≥ 20% • Platelet count ≤ 100 x 10⁹/L unrelated to therapy • Clonal evolution <p data-bbox="1083 805 1507 1065">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.</p>	<ul style="list-style-type: none"> • Blasts 10-19% of WBCs in peripheral and/or nucleated bone marrow cells • Peripheral blood basophils ≥ 20% • Persistent thrombocytopenia (< 100 x 10⁹/L) unrelated to therapy, or persistent thrombocytosis (> 1000 x 10⁹/L) unresponsive to therapy • Increasing spleen size and increasing WBC count unresponsive to therapy • Cytogenetic evidence of clonal evolution

¹Sokal JE, Baccarani M, Russo D, et al. Staging and prognosis in chronic myelogenous leukemia. Semin Hematol 1988;25(1):49-61.

²Savage 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.

³Kantarjian HM, Deisseroth A, Kurzrock R, et al. Chronic myelogenous leukemia: A concise update. Blood 1993;82:691-703.

⁴Jaffe E.S., Harris N.L., Stein H., Vardiman J.W. (Eds.): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press: Lyon 2001

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DEFINITIONS OF BLAST CRISIS

**World Health Organization
(WHO) Criteria¹**

- **Blasts \geq 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**

**International Bone Marrow
Transplant Registry²**

- **\geq 30% blasts in the blood, marrow, or both**
- **Extramedullary infiltrates of leukemic cells**

¹Jaffe E.S., Harris N.L., Stein H., Vardiman J.W. (Eds.): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press: Lyon 2001

²DeVita VT, Hellman S et al: Cancer: Principles and Practice of Oncology, 6th Edition. Vol 2., pgs 2433-2447, 2001, Lippincott, Williams & Wilkins[©]

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Discussion This manuscript is being updated to correspond with the newly updated algorithm. Last updated 12/20/07

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. In 2007, an estimated 4,570 cases will be diagnosed, and 490 patients will die from the disease.¹ The median age of disease onset is 67 years; however, CML occurs in all age groups (SEER statistics).

CML is a hematopoietic stem cell disease and it can occur in three different phases. CML is usually diagnosed in the chronic phase. Untreated CML progresses from a chronic phase to a rapidly fatal blastic phase, generally over 3 to 5 years.² The blast phase is often preceded by a transition period, called the accelerated phase, which is marked by the acquisition of new cytogenetic abnormalities in 50-80% of patients. Several definitions of the accelerated and blast phase are summarized in the algorithm.

Cytogenetic Abnormalities

CML is characterized by identification (either cytogenetic or molecular) of a clonal expansion of a hematopoietic stem cell possessing a reciprocal translocation between chromosomes 9 and 22, referred to as the Philadelphia chromosome (Ph¹). This translocation t(9;22) results in the head-to-tail fusion of the breakpoint cluster region gene (BCR) on chromosome 22 at band q11 and the ABL gene (named after the Abelson murine leukemia virus) located on chromosome 9 at band q34.³

The product of the fusion gene resulting from the t(9;22) translocation is believed to play a central role in the initial development of CML. This chimeric gene is transcribed into a hybrid BCR-ABL mRNA, producing the bcr-abl fusion protein, p210^{BCR-ABL}; this protein contains NH₂-terminal domains of BCR and the COOH-terminal domains of ABL. BCR-ABL gene encodes a protein with deregulated tyrosine kinase activity. Another bcr-abl fusion protein, p190, may be produced, but this is almost always in the setting of Philadelphia chromosome-positive (Ph¹-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-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.

Disease Monitoring

Disease monitoring is one of the key management strategies of CML to assess the response to therapy and to detect early relapse. The goal of CML therapy is to achieve complete remission, which typically progresses from hematologic remission to cytogenetic remission.

Hematologic remission is defined as the normalization of peripheral blood counts. Cytogenetic remission is determined by bone marrow aspirate and cytogenetic evaluation. Conventional metaphase cytogenetic testing for Ph¹ is widely available, relatively quick, and reliable; however, the sensitivity is approximately 5% if only 20 metaphases are examined. Cytogenetic remission, based on the absence of the Philadelphia chromosome (Ph¹), can be further evaluated by more sensitive techniques such as Fluorescence in situ hybridization (FISH)⁴ and RT-PCR (reverse transcriptase polymerase chain reaction).

Interphase or hypermetaphase FISH using *bcr-abl*-specific probes can be performed on peripheral blood specimens or marrow aspirates, respectively. Interphase FISH is fast but is associated with a background level greater than 1-5% (depending on the specific probe used in the assay); hypermetaphase FISH is more sensitive, based on the ease of analyzing up to 500 metaphases at a time. However, when patients achieve low-level FISH positivity, the technique is no longer useful for monitoring further reduction in Ph¹ levels. At this point, more sensitive techniques are required.

RT-PCR 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 $\geq 100,000$ normal cells.

The qualitative PCR technique is reported as either positive or negative. In contrast, a quantitative RT-PCR *bcr-abl* assay (QPCR)

reports the actual number of mRNA transcripts. Because of its greater sensitivity, PCR assays do not need to be obtained unless patients are Ph¹-negative by cytogenetic testing or have low levels of FISH positive cells, although earlier time points may be helpful to the clinician to establish trends in *bcr-abl* reduction. The majority of patients initially treated with imatinib or allogeneic transplant will achieve a complete cytogenetic remission, however a smaller percentage will achieve a complete molecular response identified by the absence of *bcr-abl* mRNA transcripts. Low levels of BCR-ABL mRNA transcripts are still associated with a good prognosis.^{5,6} Molecular response rates, based on QPCR, have emerged as another prognostic factor. For example, several studies have reported that a major molecular response, often defined as a greater than 3 log reduction of *bcr-abl* transcripts from a standard baseline, is associated with durable long-term remission rates.⁷⁻¹¹

Therefore, QPCR testing plays an important role in monitoring patient response in many CML patients who achieve a cytogenetic remission. QPCR will be extremely useful to determine whether levels are going up or down over time. Another advantage of QPCR is the strong correlation between results obtained from the peripheral blood and the bone marrow, allowing residual disease monitoring to be done without the necessity for obtaining bone marrow aspirations. However, even amongst academic institutions that perform this test there are differences in techniques as well as the use of various internal controls (including *bcr*; *abl*, β_2 microglobulin), that make quantization of the assay variable. A substantial effort has been made to “harmonize” *bcr-abl* testing and reporting across academic and private laboratories.¹⁰

The BCR-ABL mRNA transcripts typically fall slowly after complete cytogenetic remission is reached. The criteria for monitoring patients receiving tyrosine kinase inhibition therapy are summarized in [CML-A](#).

Tyrosine Kinase Inhibitors for CML

Imatinib mesylate

Imatinib mesylate (formerly known as STI571) is a potent and specific inhibitor of the bcr-abl tyrosine kinase and this class of drugs has revolutionized the treatment of CML.^{12,13}

Initial trials with imatinib showed a marked effect as a second line therapy in patients in chronic phase who had failed interferon-based therapy or those with more advanced stage disease (ie, accelerated phase or blast crisis).¹⁴ Newly diagnosed patients were then addressed in the IRIS (International Randomized Study of Interferon and ST1571) trial. 1106 patients were randomized to receive initial therapy with either 400 mg of daily imatinib or interferon-alpha plus low-dose cytarabine.¹⁵ Crossover was allowed for treatment failure or intolerance. With a median follow-up of 19 months, the major cytogenetic response rate at 18 months was 87.1% in the imatinib group versus 34.7% in the control group. The estimated rate of complete cytogenetic response 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.

Five year follow-up data of the IRIS trial are now available.¹⁶ Median follow-up was 60 months. Cumulative rates of complete cytogenetic response among patients receiving imatinib were 69% at 12 months and 87% at 60 months. 7% of patients had progressed to accelerated-phase CML or blast crisis. Overall survival was 89% at 60 months for patients who received imatinib as initial treatment. This data confirms 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.^{17,18}

In May 2001, imatinib mesylate was first approved by the FDA (Food and Drug Administration) 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.

Dasatinib

Dasatinib (formerly known as BMS-354825) is an 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.¹⁹

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.²⁰ 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 within 3-6 months or absence of a major cytogenetic response 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. Results from these clinical studies were available initially in the abstract form and are now published in peer reviewed literature.

In the START-C trial, patients with imatinib-resistant or intolerant chronic phase CML (CP-CML) were treated with dasatinib (70 mg twice daily).²¹ An initial result of this study for 186 patients revealed that complete hematologic response (CHR) was observed in 90% of patients. Dasatinib also induced major cytogenetic response (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%.

START-A trial evaluated the safety and efficacy of dasatinib in patients with imatinib resistant or intolerant accelerated phase CML (AP-CML).²² Results are reported for the first 107 patients enrolled in the study. At 8-month follow-up, major hematologic response (MaHR) was achieved in 64% of patients and major cytogenetic response (MCyR) was achieved in 33% of the treated population and 76% of patients remained progression-free.

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.²³ In the first 74 patients with MBC-CML, 32% had achieved MaHR at 6-month follow-up which increased to 34% at 8-month follow-up. MCyR was achieved in 31% of patients. In the LBC-CML group, out of the first 42 patients evaluated, 31% achieved MaHR at 6-month follow-up, and this rate was maintained at 8-month follow-up. MCyR was achieved in 50% of patients.

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. Nonhematologic adverse events were mild to moderate and cytopenias although more common were manageable with dose modification.

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 no longer responding to or who can no longer tolerate imatinib (www.sprycel.com).

In a recent dose-optimization randomized study, dasatinib dosed at 100 mg once daily was equally effective as 70 mg twice daily, and associated with a lower incidence of pleural effusion, thrombocytopenia, and toxicity-related discontinuation (6% vs. 15%) in patients with CP-CML who were resistant or intolerant to imatinib.²⁴ Based on the results of this study, FDA has approved 100 mg once daily as the starting dose for patients with CP-CML. The recommended starting dose for patients with accelerated or blast phase CML is 70 mg twice daily.

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, in imatinib resistant (20-50 times more potent) as well as imatinib sensitive (3-7 times more potent) CML cell lines. In a phase I study, nilotinib was found to be active in imatinib resistant CML with a favorable safety profile.²⁵

Following this study, the safety and efficacy of nilotinib was evaluated in a phase II open label trial in imatinib resistant or intolerant CP-CML and AP-CML patients. Nilotinib was administered at 400 mg twice daily. The efficacy endpoint for CP-CML was MCyR and the endpoint for AP-CML was major hematologic response (MHR). The results from an interim analysis conducted on 280 patients with CML-CP at 6-month follow-up were reported recently.²⁶ MCyR was observed in 48% of patients and CCyR was observed in 31% of patients. In patients with AP-CML, hematological response was observed in 47% of patients and MCyR was observed in 29% of patients. Overall survival rate among the 119

patients after 12 months of follow-up was 79%. Non-hematologic adverse events were mostly mild to moderate.²⁷

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 CP-CML. QTc prolongation was the major nonhematologic adverse reaction associated with nilotinib, which could be managed with dose reduction. Electrocardiograms (ECGs) should be obtained to monitor QTc.

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.

Chronic Phase CML (CP-CML)

Initial Workup

The panel recommended the following tests as part of the initial evaluation of CP-CML:

- History and physical (H&P)
- Complete blood count (CBC)
- Platelet count
- Chemistry profile
- Bone marrow aspirate and biopsy, including morphologic review of the percentage of blasts and basophils, and cytogenetic analysis, including FISH and PCR (only if a quantitative PCR is available).

Bone marrow cytogenetics and measurement of BCR-ABL transcript numbers by PCR is recommended before initiation of treatment as well as for assessing the response to therapy ([CML-A](#)).^{28,29} 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 with BCR-ABL-negative disease have a significantly worse prognosis than those with BCR-ABL -positive disease.³⁰ Patients who are BCR-ABL-negative do not have CML. Therefore, for patients with BCR-ABL-negative disease further evaluation for other diseases is warranted. Patients whose cells are BCR-ABL-positive (by karyotype analysis, FISH or molecular techniques) are the focus of this NCCN guideline.

Primary Treatment

NCCN guidelines recommend primary treatment with imatinib mesylate for newly diagnosed patients with Ph1 or BCR-ABL positive chronic phase CML. The option of participating in a clinical trial should be discussed with the patient. Most of 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 complete cytogenetic response 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. Imatinib mesylate at a standard dose of 400 mg daily is a category 1 recommendation for initial treatment of CML. In very rare patients who are not able to tolerate imatinib, interferon therapy or participation in a clinical trial can be considered.

High-dose imatinib

Most patients retain variable levels of residual molecular disease at the 400 mg dose of imatinib. Therefore, higher doses of imatinib, up to 800 mg/day, have also been investigated. In a case series of 114 newly diagnosed patients were treated with 400 mg imatinib twice daily. 96%

had a major cytogenetic response and 90% (Ph < 35%) had a complete cytogenetic response (Ph 0%).³¹ Compared with standard dose imatinib, high dose imatinib was associated with significantly better complete cytogenetic response rate (P=.0005), major molecular response rate (QPCR<0.05%; P=.00001), and complete molecular response rate (undetectable bcr-abl; P=.001). High dose imatinib was well tolerated but did result in more frequent myelosuppression; nevertheless, 82% of patients continued to receive 600 mg or more of imatinib daily. With a median follow-up of 15 months, no patient had progressed to accelerated or blastic phase. Similar results were reported in a long term-follow up study which included patients from three sequential trials.³²

Although resistance to imatinib has developed in patients in late chronic phase initially treated with interferon, little evidence of imatinib resistance has been seen in patients treated at the time of diagnosis. Some studies on imatinib therapy showed that dose escalation of imatinib might also overcome imatinib-associated resistance.³³⁻³⁶ However, further follow-up is clearly warranted in this setting.

Several ongoing studies are focusing on dose escalation of imatinib in newly diagnosed patients. There is also interest in exploring higher doses in patients with poor prognostic features, such as those with high risk Sokal scores, a prognostic staging system for CML. Increased efficacy of higher dose imatinib has not yet been demonstrated in randomized trials. Higher dose imatinib for newly diagnosed patients is considered a 2A recommendation.

Imatinib Toxicity

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.³⁷ Hematologic and non-hematologic toxicities caused by imatinib, as well as specific, panel-recommended interventions, are summarized in the algorithm. Erythropoietin has been shown to be effective in patients who develop imatinib-associated anemia.³⁸

Cardiotoxicity

In a recent trial, long term imatinib treatment was associated with congestive heart failure (CHF) and cardiotoxicity. 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.³⁹ After a median follow-up of 47 months, 22 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.

Imatinib and Pregnancy

Imatinib has been shown to be teratogenic and embryotoxic in animal studies, but the effect of imatinib during conception and pregnancy are not known. Pye et al. recently reported the outcome of pregnancies in 180 women exposed to imatinib during pregnancy.⁴⁰ 50% of pregnancies with known outcome were normal. 10% of pregnancies with known outcome had fetal abnormalities. 18 pregnancies ended in spontaneous abortion. In a recent report of 10 women who discontinued imatinib due to pregnancy, 6 had increase in Ph-positive metaphases. 18 months after resuming therapy, only 3 women had complete cytogenetic response.⁴¹ At the present time enough evidence is not available to favor the continuation of imatinib during pregnancy. Potential benefit of imatinib therapy for the mother or its potential risk to the fetus must be carefully evaluated on an individual basis prior to administering imatinib for pregnant women.

Imatinib Monitoring

Data suggest that the number of BCR-ABL transcripts, as measured by QPCR, is associated with progression free survival after treatment with imatinib. In the IRIS trial, BCR-ABL transcripts were measured in the blood of all patients who had a complete cytogenetic remission. Among patients in the imatinib group, the median transcript level was significantly lower 18 months after complete cytogenetic remission as compared to 12 months afterwards ($P=.002$). A similar difference was also seen if a frequency of a reduction of at least 3-log was examined at 12 and 18 months (69% vs 81%, $P=.003$). For patients receiving imatinib who had a reduction in BCR-ABL transcripts of at least 3-log at 12 months (defined as a major molecular response), the probability of remaining progression free was 100% at 19 months, as compared with 95% for patients who had a complete cytogenetic remission with a reduction of less than 3-log, and 85% for patients who did not have a complete cytogenetic response ($P<0.001$). In the 5 year data update from the IRIS trial, no patients with a major molecular response by 12 months progressed to accelerated or blast phase with a 54 month follow-up.

Most patients receiving imatinib as initial treatment for CML will achieve a complete cytogenetic response; therefore, more sensitive testing for residual disease is an important part of monitoring. BCR-ABL transcript levels should be measured every 3 months when the patient appears to be responding to imatinib, and when a complete cytogenetic remission is reached. Cytogenetic evaluation is recommended at 6 and 12 months when the patient appears to be responding to treatment, decreasing to every 12 months when complete cytogenetic response is reached. If the patient is not in a complete cytogenetic remission at 12 months, repeat cytogenetic testing is recommended at 18 months.

Cytogenetic testing could be considered in patients without any early evidence of relapse on the basis of FISH or QPCR since chromosomal

abnormalities may emerge in Philadelphia negative cells.⁴²⁻⁴⁴ For example, in a case series of 1001 patients treated with imatinib, clonal abnormalities were detected in 34.⁴⁵ Another case series reported clonal abnormalities and in 21 of 342 patients.⁴⁴ The significance of these chromosomal abnormalities is unclear, but of note is that the most common abnormality is trisomy 8, an aberration frequently seen in myelodysplastic syndrome. Only rare cases of myelodysplastic syndrome have been reported in patients with CML and these were usually in patients who had received interferon as well as prior chemotherapy. Some series have reported these abnormalities in only a small percentage of metaphases and have also noted that on subsequent examination these abnormalities may disappear. Thus, at this point, the significance of these aberrations is unclear and further follow-up is clearly indicated.

Some patients will eventually develop secondary resistance which may be related to mutations in the BCR-ABL fusion mRNA, resulting in conformational changes in the fusion protein that affect the binding site of imatinib on the tyrosine kinase. Identification of mutations supports the diagnosis of imatinib resistance and suggests that the patient should be switched to dasatinib, be considered for allogeneic transplant, or placed on a clinical trial of another tyrosine kinase inhibitor, such as nilotinib.⁴⁶⁻⁵¹ However, patients who develop a T315I mutation usually do not respond to dasatinib or nilotinib, and thus should be considered for transplantation or a clinical trial.

Currently there are no guidelines for changing therapy based on rising BCR-ABL transcripts as detected by QPCR. A rising bcr-abl level may be associated with an increased risk of the emergence of an abl mutation in the future.⁴⁸ In such situations, ABL kinase domain (KD) mutational analysis may provide additional information. Thus, a rising bcr-abl level should prompt a bone marrow aspirate for cytogenetic evaluation, sequencing of the abl tyrosine kinase domain, and careful

monitoring of peripheral blood bcr-abl. Changes of therapy based solely on a rising bcr-abl level should be done under the auspices of a clinical trial.

Discontinuation of Imatinib

Imatinib has become a standard front-line treatment for patients with CML. Complete cytogenetic responses can be achieved in most patients with CP-CML. However, the disease usually relapses if imatinib therapy is stopped even in patients who achieved complete response.⁵² At the present time discontinuation of therapy is not recommended for patients who achieve a molecular remission with imatinib.

Follow-up Therapy in Patients Receiving Imatinib

3 and 6 Month Follow-up

After three months of imatinib therapy, patients are categorized according to whether or not hematologic remission is present. The guidelines recommend dasatinib or nilotinib as one of the treatment options for patients with no hematologic remission or if they are in hematologic relapse. Other treatment options include an allogeneic transplant or participation in a clinical trial.

Those in hematologic remission continue on the same dose of imatinib and are reevaluated at 6 months with bone marrow cytogenetics. . Patients are then classified into the following categories: complete, partial or minor cytogenetic response, or no cytogenetic response or cytogenetic relapse. Those with a complete cytogenetic response continue on the same dose of imatinib. However, dose escalation of imatinib to a maximum dose of 600-800 mg, as tolerated, may be considered in those with a partial or minor cytogenetic response. Patients with no cytogenetic response or in relapse can be switched to dasatinib or nilotinib. Alternatively, they can be treated with increased

dose of imatinib. Allogeneic transplant or participation in a clinical trial are alternative options.⁵³ Interferon with or without cytarabine is no longer recommended.

12 and 18 Month Follow-up

Patients are evaluated again with bone marrow cytogenetics at 12 months, and are categorized as having complete, partial, and minor or no cytogenetic response. Once again, if a complete cytogenetic response is detected, the same dose of imatinib is continued, dose escalation is considered if there is a partial cytogenetic response. Increased dose of imatinib, if tolerated, dasatinib or nilotinib, allogeneic transplant or participation in a clinical trial can be considered for those with a minor or no cytogenetic response, or a cytogenetic relapse. Given the availability of dasatinib, continuation of imatinib to maintain hematologic remission is no longer recommended for those with a minor cytogenetic response.

Patients are further evaluated cytogenetically at 18 months, with continuing imatinib for those in complete cytogenetic response, and for those with partial response, options include increased dose of imatinib, if possible, a switch to dasatinib or nilotinib, allogeneic transplant or participation in a clinical trial.

Disease Progression While on Imatinib

Disease progression is defined as loss of hematologic or cytogenetic response or progression to accelerated phase (AP-CML) or blast crisis (lymphoid or myeloid). A phase II trial was conducted in which patients with imatinib resistant CP-CML were randomized to receive 140 mg of dasatinib or 800 mg of imatinib.⁵⁴ Median follow-up was 15 months. CHR was observed in 93% of patients receiving dasatinib compared to 82% of patients randomized to high dose imatinib. Dasatinib also showed higher MCyR (52% vs. 33%, $P = 0.023$) and higher major molecular responses (16% vs. 4%, $P = 0.038$). 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. Treatment failure and progression-free survival were favorable for dasatinib, indicating that dasatinib is an effective treatment for CP-CML resistant to conventional imatinib doses.

No uniform consensus was reached about the definition of accelerated phase; therefore, 4 different definitions are provided in the guidelines.⁵⁵⁻⁵⁸ According to the International Bone Marrow Transplant Registry, blast crisis is defined as 30% or greater blasts in the blood, bone marrow, or both, or as the presence of extramedullary disease.⁵⁸ The World Health Organization (WHO) criteria for blast crisis have also been incorporated into the algorithm.⁵⁸

Dasatinib or nilotinib, followed by allogeneic transplant, if feasible, is recommended for disease progression to accelerated phase CML following imatinib therapy or for chronic phase CML that is refractory to imatinib, whereas only dasatinib followed by allogeneic transplant is recommended for patients who progress to blast phase on imatinib therapy. Participation in a clinical trial is another option for all patients with progressive disease.

Alternatively, ALL-type induction therapy is appropriate for those with a lymphoid blast crisis (LBC), while an AML-type induction therapy is appropriate for those with a myeloid blast crisis (MBC). See [NCCN AML Guidelines](#) for treatment options. CML in lymphoid blast crisis is pathologically similar to Ph-positive ALL. In patients presenting with de novo Ph-positive ALL, imatinib or dasatinib can be given in combination with chemotherapy.^{59,60,61}

Allogeneic Stem Cell Transplant

Allogeneic stem cell transplant (SCT) 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. The widespread application of hematopoietic stem cell transplant (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. 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.

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. Indeed, two studies have shown similar outcomes for transplantation for patients with chronic phase CML using either a fully matched related or unrelated donor, with 5-year survival rates greater than 70% for patients age 50 years or younger who receive transplants within a year of diagnosis.^{62,63} Investigational approaches using non-myeloablative “minitransplants” have been pioneered to engender a graft-versus-leukemia effect without exposing the patient to the toxicity associated with the myeloablative preparative regimen. These studies are still investigational but are quite promising and show that “molecular remissions” may be achieved in patients with CML.⁶⁴⁻⁶⁸

Patient age, disease phase and duration, and therapy before transplantation influence the outcome of allogeneic transplant. Age older than 50 years is associated with decreased survival after an unrelated transplant, but an age effect is much less pronounced in the matched-related setting.^{62,63,69} Most centers show an improved outcome

for early transplantation in chronic phase, with transplantation within the first 1 to 2 years from diagnosis producing superior outcomes when compared with transplantation more than 2 years from diagnosis.^{62,69}

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.^{69,70}

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.⁷¹⁻⁷³ Indeed some studies suggested that previous imatinib treatment might lead to increased regimen-related toxicity after transplant, especially liver toxicity,^{74,75} while other studies suggested no increase in toxicity.^{76,77} Of note is that these studies include very heterogeneous groups concerning diagnosis (CML and ALL), phase, and transplant regimen. A recent large retrospective study compared the transplant outcomes of 233 patients who had not received imatinib prior to transplant, with 145 who had various exposures to imatinib.⁷⁸ There was no significant difference between the two groups regarding death, relapse rate and non-relapse mortality. These data suggest that pre-transplant imatinib does not compromise the outcome of a subsequent allogeneic transplant. NCCN recommendations for Allogeneic SCT

Chronic phase CML

NCCN recommendations have changed since the 5-year follow-up data of IRIS trial showed excellent survival benefit for imatinib. Allogeneic SCT is no longer recommended as a first-line treatment for chronic phase CML, however, it can be considered in very rare cases. Role of HSCT in the treatment of CML should be discussed with the patient. In rare cases where allogeneic SCT is an option, HLA testing should be performed prior to transplantation. Nonmyeloablative transplant is

investigational and it should be performed only in the context of a clinical trial.

Allogeneic SCT may be recommended for those who are not in remission or in hematologic relapse after 3-months following primary treatment with imatinib. Allogeneic SCT can also be considered for those who have no cytogenetic response or those in cytogenetic relapse at 6, 12 or 18 months after achieving initial hematologic remission, especially those with a T315I mutation.

Disease Progression

Allogeneic SCT is an immediate consideration in patients presenting with accelerated phase or blast crisis CML. Since these patients have progressed on imatinib therapy, treatment with a course of dasatinib as a “bridge” to transplantation will be beneficial for these patients.

In summary, the NCCN guidelines have included allogeneic SCT as an alternative treatment option for the following patients:

- In patients who do not achieve hematologic remission after three months of imatinib therapy.
- In patients with no cytogenetic response or those in cytogenetic relapse at 6, 12 or 18 months, after achieving initial hematologic remission after 3 months of imatinib therapy.
- In patients progressing on imatinib to accelerated phase or blast crisis.

Follow-up therapy for patients receiving allogeneic transplant

Donor lymphocyte infusion (DLI) is effective in inducing remissions in patients with relapsed CML following allogeneic SCT, though it is more effective in chronic phase than advanced phase.⁷⁹ DLI induces complete remissions in majority of patients with CML in early-stage relapse.⁸⁰ 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 the 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 (RIC) regimens have reduced the incidence of GVHD.^{81,82}

Recently imatinib has been shown to very effective in inducing remissions, particularly in patients with relapsed chronic phase CML following allogeneic SCT.⁸³⁻⁸⁷ However, in a recent retrospective analysis, disease-free survival was significantly higher for DLI than in the imatinib group.⁸⁸ There was also a trend towards higher rates of complete molecular remissions in the DLI group, suggesting that treatment with imatinib alone is not curative for relapsed CML following allogeneic SCT.

These observations are yet to be confirmed in randomized trials. There are no data to support the use of post transplant imatinib in patients who have previously failed on imatinib. Other tyrosine kinase inhibitors like dasatinib or nilotinib may be more appropriate, although there is no published data to support its use in post transplant.

NCCN recommendations

The guidelines divide patients into two groups following allogeneic SCT: those who have achieved cytogenetic remission and those who are not in remission or in cytogenetic relapse.

Relapsed Disease

Patients who relapse are categorized according to the presence or absence of GVHD. Those with GVHD may be treated with imatinib or dasatinib. Participation in a clinical trial is another option. In patients without GVHD, a monitored withdrawal of immune suppression is recommended to induce GVHD and the graft-versus-leukemia effect. Patients who respond to immunosuppression with cytogenetic

remission can be followed by PCR; repetitive PCR negativity warrants observation. If the PCR remains positive for residual disease, patients may be treated with imatinib, nilotinib or dasatinib. Treatment options for patients who do not achieve a complete cytogenetic response after immunosuppression include imatinib, nilotinib or dasatinib, interferon,⁸⁹ DLI or participation in a clinical trial.

Remission

Patients in cytogenetic remission after allogeneic transplant are followed with PCR monitoring to determine the presence or absence of bcr-abl. The guidelines recommend PCR monitoring every 3 months for 2 years, then every 6 months for 3 years. A qualitative assay positive for bcr-abl is associated with a high risk of relapse, especially 6 to 12 months after transplant and in the setting of T-cell depletion.^{90,91} If a qualitative PCR is positive with positive cytogenetic results, then the relapsed disease is considered present, and the patient is treated as described above for relapsed disease.

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 recommended first-line treatment for newly diagnosed chronic phase CML, at an initial standard dose of 400 mg daily. Higher doses, if tolerated can be administered for patients who are in relapse. Disease monitoring with cytogenetics and PCR is crucial in CML to assess response to treatment.

Some patients will eventually develop secondary resistance related to the presence of mutation in the BCR-ABL gene, resulting in disease progression on imatinib. Second-line tyrosine kinase inhibitors such as dasatinib and nilotinib have been found to be safe and effective in patients with imatinib resistant or intolerant CML. Dasatinib or nilotinib is a treatment option for those who progress to accelerated phase on imatinib therapy or for those with chronic phase CML that is refractory to imatinib, whereas only dasatinib is recommended for patients who progress to blast phase on imatinib therapy.

Allogeneic stem cell transplant (SCT) is the only potentially curative treatment for patients with CML, but the advent of imatinib has challenged the role of transplant as first-line therapy. Allogeneic SCT is essential only for patients have inadequate or no responses to imatinib therapy, as well as for those who progress on imatinib.

Treatment options for CML with kinase inhibitors depend on the stage of the disease, the agent's side effect profile and its relative effectiveness against BCR-ABL mutations. Availability of more potent kinase inhibitors has widened the treatment options for CML and the outlook for patients with CML continues to look promising.

Disclosures for the NCCN Chronic Myelogenous Leukemia Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed the names of companies, foundations, and/or funding agencies from which they received research support; for which they participate in speakers' bureau, advisory boards; and/or in which they have equity interest or patents. Members of the panel indicated that they have received support from the following: Bristol-Myers Squibb, Genzyme, Novartis, PDL BioPharma and Vion Pharmaceuticals, Inc. Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest

as sufficient reason to disallow participation in panel deliberations by any member.

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