National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Chronic Myelogenous Leukemia

V.2.2007

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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 Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Consensus

Summary of Guidelines Updates

Summary of the Guidelines updates

The changes in the 2.2007 version of the Chronic Myelogenous Leukemia guidelines from the 1.2007 version is the addition of the updated manuscript representing the changes to the algorithm.

Summary of the changes in the 1.2007 version of the Chronic Myelogenous Leukemia guidelines from the 1.2006 version include:

- In the Primary Treatment of CML, higher doses of imatinib may be considered in some patients. This was added as footnote f with a supporting reference (CML-1).
- Footnote h was modified to include the consideration of IFN for rare patients not able to tolerate dasatinib (CML-1).
- After the 3-month evaluation, the recommendations for patients not in hematologic remission, or in hematologic relapse were changed to "Dasatinib and reconsider HSCT or clinical trial" (CML-2).
- After the 6-month evaluation, the recommendations for patients with no cytogenetic response or cytogenetic relapse were modified to include Dasatinib. IFN was removed as a treatment option (CML-2).
- After the 12-month evaluation, the recommendations for patients with a partial cytogenetic response were modified with the removal of HSCT and clinical trial as treatment options (CML-3).
- After the 12-month evaluation, the recommendations for patients with a minor or no cytogenetic response or cytogenetic relapse were modified to include Dasatinib. IFN was removed as a treatment option (CML-3).
- The 18-month evaluation and treatment options are new recommendations (CML-3).
- Patients treated with HSCT as primary therapy, not in remission, or in relapse, and a complete cytogenetic response after monitored withdrawal of immune suppression in the setting of No GVHD; the treatment recommendations are now based on the PCR result. PCR negative patients, the recommendation is observation. PCR positive patients, the recommendation is for imatinib and DLI for progression.(CML-4).
- Patients treated with HSCT as primary therapy, not in remission, or in relapse, and GVHD; IFN was removed as a treatment recommendation (CML-4).
- For patients with disease progression on imatinib therapy, Dasatinib followed by HSCT was added as a treatment recommendation for patients in accelerated phase or blast crisis. (CML-5).
- Monitoring for Patients Receiving Tyrosine Kinase Inhibitor Therapy is a new attachment (CML-A) and replaces the previous Monitoring During Therapy attachment.
- Management of Dasatinib Toxicity is a new attachment (CML-D).

Chronic Myelogenous Leukemia

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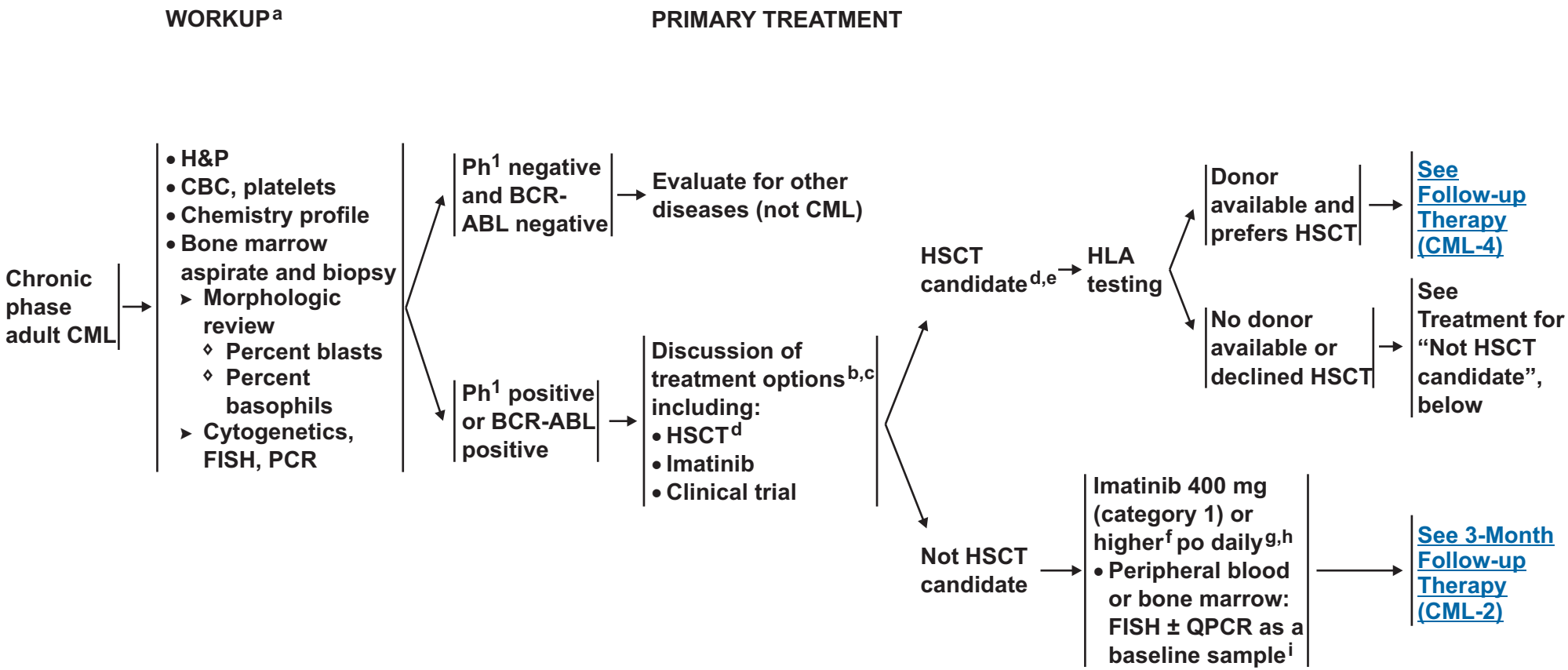

[a] See Monitoring for Patients Receiving Tyrosine Kinase Inhibitor therapy (CML-A).

[b] HSCT has definite survival benefits whereas, despite very promising early responses, the survival benefit, long term toxicities, and durability of response of imatinib are unknown. Interferon has been shown to produce inferior short term responses compared to imatinib, although long term comparisons of effect are still not available. The majority of NCCN institutions recommend imatinib as the primary treatment option in patients who do not undergo HSCT.

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

[d] HSCT = hematopoietic stem cell transplantation. Refers to a matched related and unrelated allogeneic transplant.

[e] 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.

[f] Consider higher doses in some patients. 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.

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

[h] Rare patients unable to tolerate imatinib mesylate or dasatinib, then consider IFN.

[i] For monitoring at 12 mo and thereafter.

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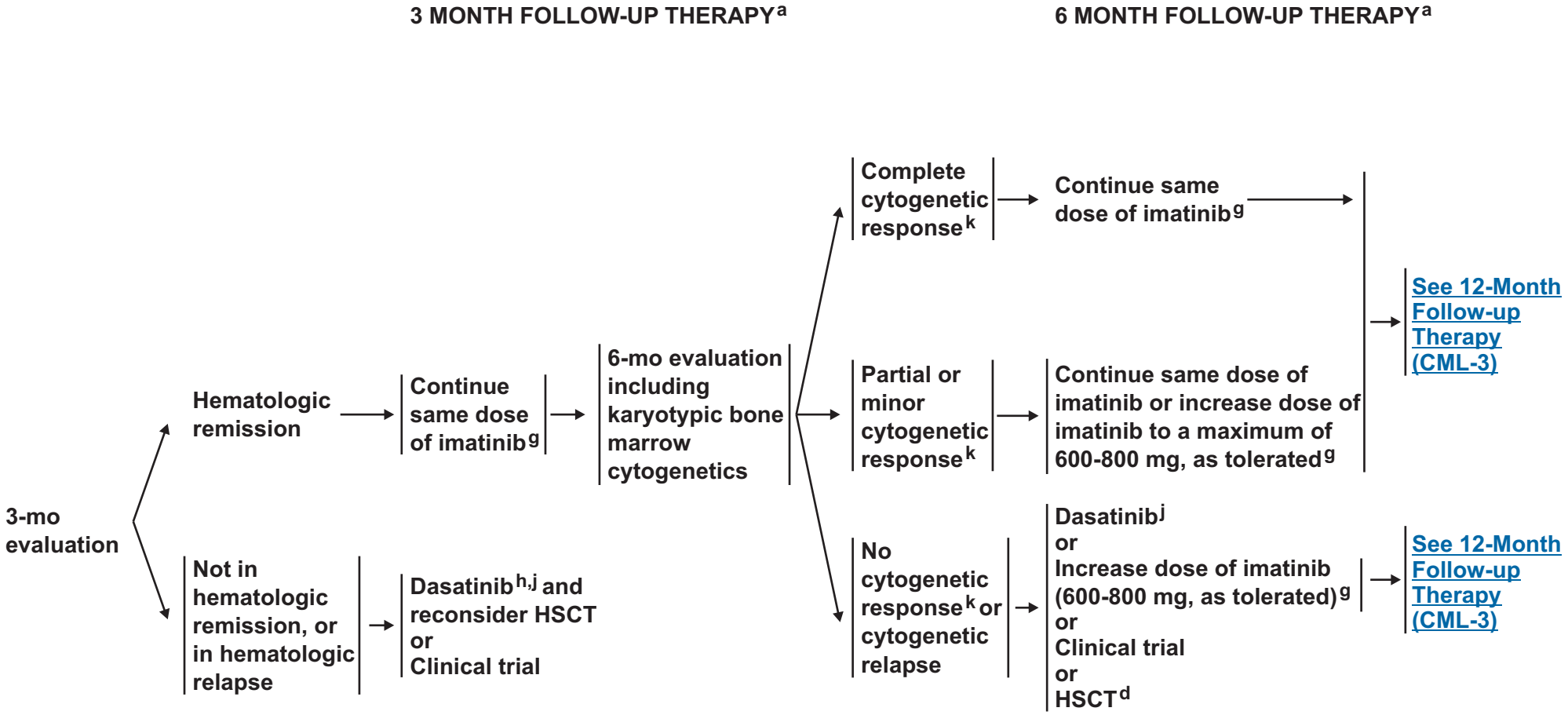
Chronic Myelogenous Leukemia



[a] See Monitoring for Patients Receiving Tyrosine Kinase Inhibitor therapy (CML-A).
[d] HSCT = hematopoietic stem cell transplantation. Refers to a matched related and unrelated allogeneic transplant.
[g] See Management of Imatinib Toxicity (CML-C).
[h] Rare patients unable to tolerate imatinib mesylate or dasatinib, then consider IFN.
[j] See Management of Dasatinib Toxicity (CML-D).
[k] See Criteria for Cytogenetic and Hematologic Response (CML-E).

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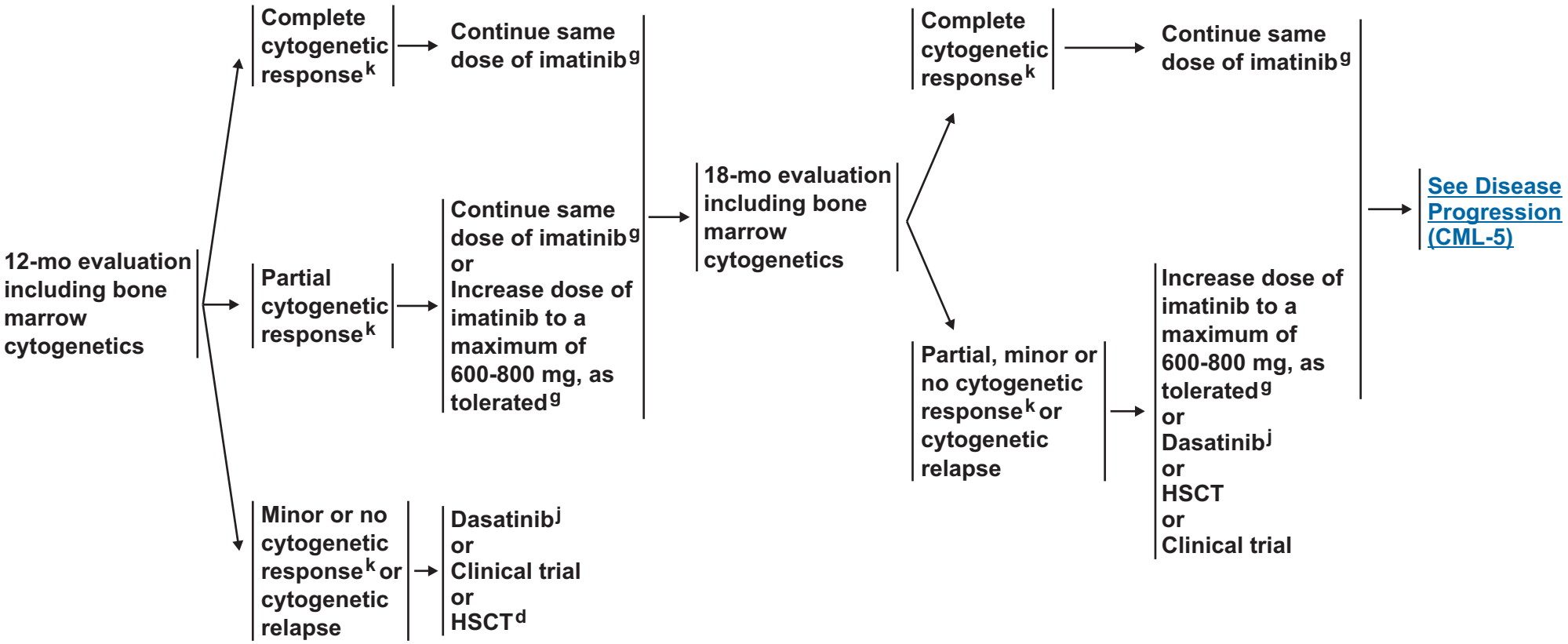
Chronic Myelogenous Leukemia

12 MONTH FOLLOW-UP THERAPY[a]



[a] See Monitoring for Patients Receiving Tyrosine Kinase Inhibitor therapy (CML-A).
[d] HSCT = hematopoietic stem cell transplantation. Refers to a matched related and unrelated allogeneic transplant.
[g] See Management of Imatinib Toxicity (CML-C).
[j] See Management of Dasatinib Toxicity (CML-D).
[k] See Criteria for Cytogenetic and Hematologic Response (CML-E).

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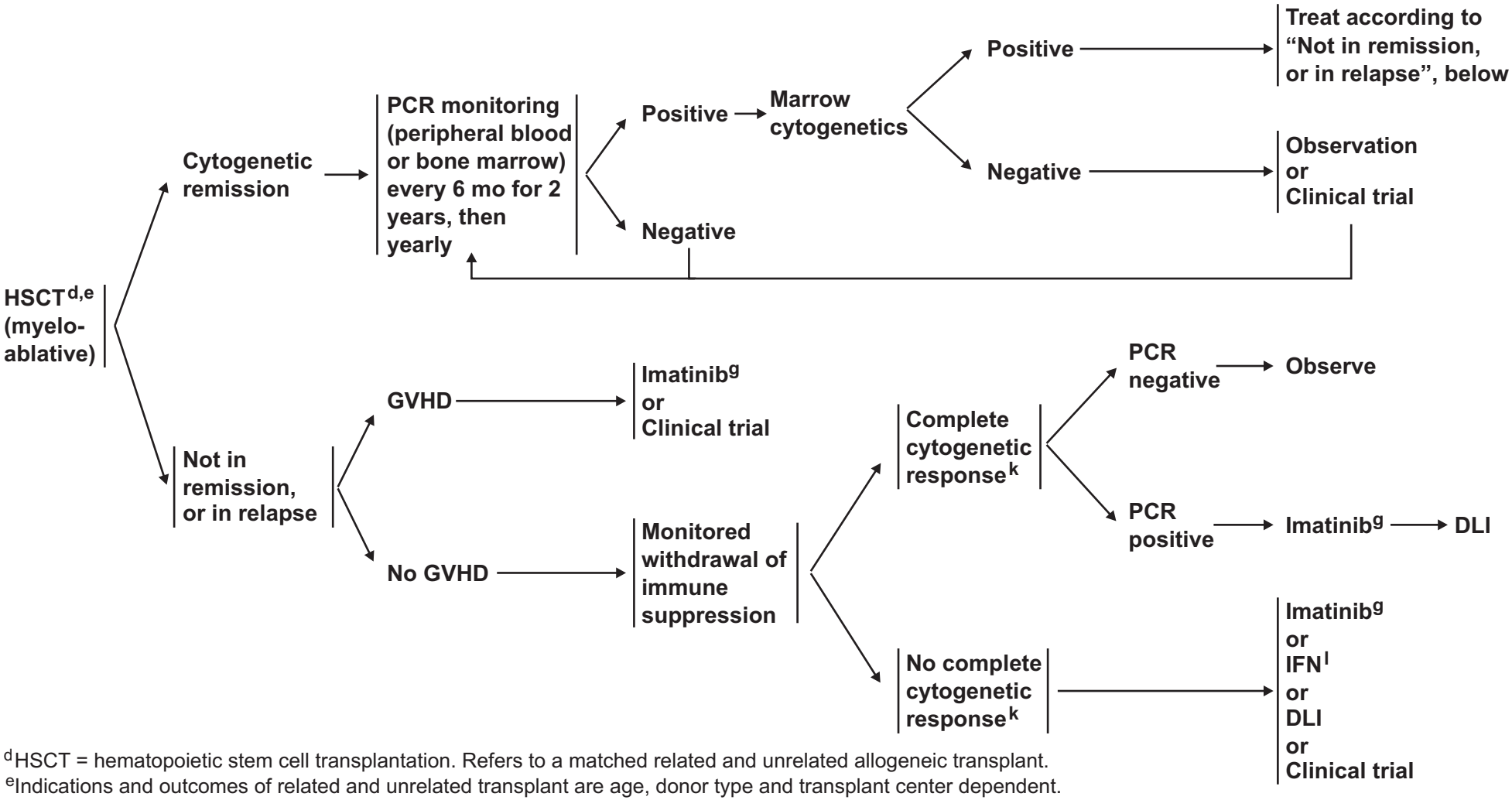
Chronic Myelogenous Leukemia

PRIMARY TREATMENT **FOLLOW-UP THERAPY**



[d] HSCT = hematopoietic stem cell transplantation. Refers to a matched related and unrelated allogeneic transplant.
[e] 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.
[g] See Management of Imatinib Toxicity (CML-B).
[k] See Criteria for Cytogenetic and Hematologic Response (CML-E).
[l] See Management of IFN Toxicity (CML-F).

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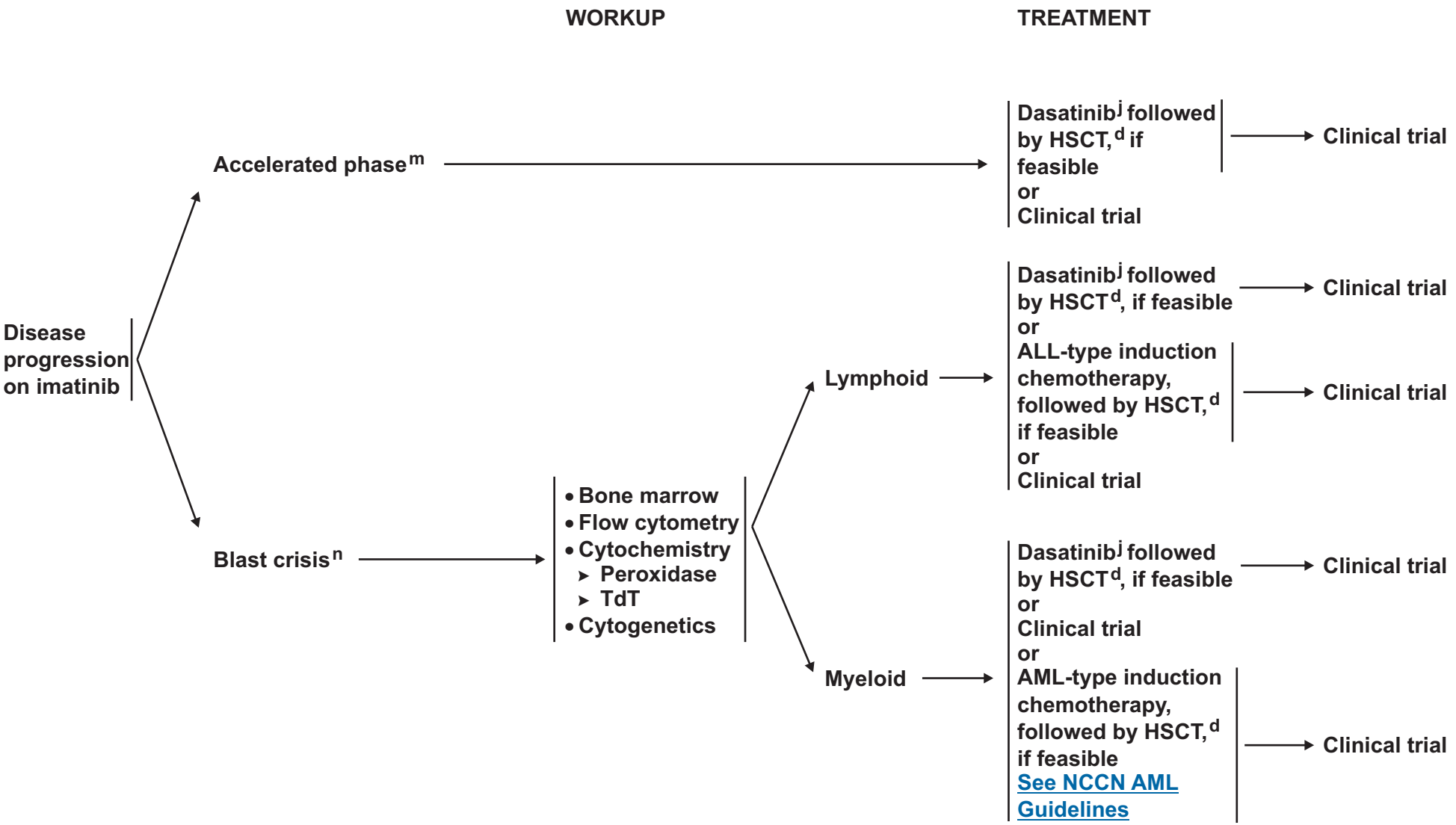
Chronic Myelogenous Leukemia



[d] HSCT = hematopoietic stem cell transplantation. Refers to a matched related and unrelated allogeneic transplant.
[j] See Management of Dasatinib Toxicity (CML-D).
[m] See Definitions of Accelerated Phase (CML-G).
[n] See Definitions of Blast Crisis (CML-H).

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MONITORING FOR PATIENTS RECEIVING TYROSINE KINASE INHIBITOR THERAPY[1]

Indications for cytogenetics and PCR for BCR-ABL mRNA

At diagnosis of CML

- Bone marrow cytogenetics and measurement of BCR-ABL transcript numbers by PCR 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.
- Bone marrow cytogenetics at 18 months if patient not in a complete cytogenetic remission (CCR) at 12 months.

When a patient reaches complete cytogenetic remission (CCR)

- BCR-ABL transcript levels should be measured every 3 months.
- Bone marrow cytogenetics every 12 months.

When a patient appears to have rising level of BCR-ABL transcripts

- Rising levels should be confirmed by two measurements not more than a month apart.
- If a rising level of BCR-ABL transcripts is confirmed, the frequency of measurement should be increased to once a month.
- Mutation testing should be performed (see below).

Indications for ABL kinase domain (KD) mutation analysis

Chronic phase CML

- ABL KD mutation screening is indicated 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).

Accelerated and blast phase CML

- Testing for KD mutations should be carried out routinely at 3 month intervals in high-risk patients, regardless of level of response to TK inhibitors.

[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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Chronic Myelogenous Leukemia

MANAGEMENT OF IMATINIB TOXICITY (PAGE 1 of 3)[1]

Hematologic[2]

- Grade 3-4 neutropenia (neutrophil count < 1000/mm^3):
  - Add growth factor, titrate to maintain neutrophil count above 1000.
    or
  - Hold drug until grade 2 or better, resume at the same dose if grade 2 reached within 2 wks or at 25-33% dose reduction (not less than 300 mg) if grade 3-4 persisted more than 2 wks.[3]
- Grade 3-4 thrombocytopenia (platelet count < 50,000/mm^3):
  - Hold drug until grade 2 or better, resume at the same dose if grade 2 reached within 2 wks or at 25-33% dose reduction (not less than 300 mg) if grade 3-4 persisted more than 2 wks.[3]
- Grade 3-4 anemia: Erythropoietin (See the NCCN Cancer and Treatment-Related Anemia Guidelines)
- In accelerated phase, patients may have cytopenias related to disease, it is not necessary to discontinue or hold imatinib

Specific Interventions

- Diarrhea: supportive care
- Edema: diuretics, supportive care
- Fluid retention: diuretics, supportive care, dose reduction, interruption or discontinuation
- 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).

Nonhematologic - Liver

Grade $\geq$ 2, hold drug until grade $\leq$ 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.

[1] Many toxicities are self-limiting, consider re-escalating dose at a later time.
[2] If patient remains nonresponsive with erythroid or myeloid therapy, consider obtaining bone marrow.
[3] 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.

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)[4]

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
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.

[4] Demetri GD, Benjamin R, Blanke CD, et al. NCCN Task Force Report : Optimal management of patients with gastrointestinal stromal tumor (GIST)---Expansion and Update of NCCN Clinical Practice Guidelines. JNCCN 2004;2(suppl1):S1-S26.

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

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POTENTIAL DRUG INTERACTIONS WITH IMATINIB (3 of 3)[4]

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.

[4] Demetri GD, Benjamin R, Blanke CD, et al. NCCN Task Force Report : Optimal management of patients with gastrointestinal stromal tumor (GIST)---Expansion and Update of NCCN Clinical Practice Guidelines. JNCCN 2004;2(suppl1):S1-S26.

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MANAGEMENT OF DASATINIB TOXICITY (1 of 2)

Hematologic

- Grade 3-4 neutropenia (neutrophil count < 1000/mm^3):
  - Add growth factor, titrate to maintain neutrophil count above 1000.
    or
  - Hold drug until grade 2 or better, resume at the same dose if grade 2 reached within 7 days or reduce one dose level if grade 3-4 persisted more than 7 days.
- Grade 3-4 thrombocytopenia (platelet count < 50,000/mm^3):
  - Hold drug until grade 2 or better, resume at the same dose if grade 2 reached within 7 days or reduce one dose level if grade 3-4 persisted more than 7 days.
- Grade 3-4 anemia: Erythropoietin (See the NCCN Cancer and Treatment-Related Anemia Guidelines)
- In accelerated phase, patients may have cytopenias related to disease, it is not necessary to discontinue or hold dasatinib

Specific Interventions

- Edema: 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 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 at decreased dose level

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

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

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POTENTIAL DRUG INTERACTIONS WITH DASATINIB (2 of 2)

Caution is warranted when administering dasatinib to subjects taking drugs that are highly dependent on CYP3A4 for metabolism and have a narrow therapeutic index. Systemic exposures to these medications could be increased while receiving dasatinib. In in vitro studies, dasatinib is a strong inhibitor of the human CYP3A4 enzyme and a weak inhibitor of CYP1A2, CYP2D6 and CYP2C19.

Until information regarding exposure-toxicity and exposure-response relationships is available with dasatinib, concomitant CYP3A4 inhibitors and inducers should be avoided, if possible, since they could alter the systemic exposure to dasatinib.

Medications associated with QT prolongation that should be avoided include:

- **quinidine, procainamide, disopyramide**
- **amiodarone, sotalol, ibutilide, dofetilide**
- **erythromycins, clarithromycin**
- **chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide**
- **cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine**

In vitro solubility data indicate that dasatinib may have decreased solubility and absorption at pH > 4. Until further data are available, patients should try to avoid taking proton pump inhibitors and H_2 antagonists. Short-acting antacid agents may be taken, but is recommended that these not be taken from 4 hours before to 4 hours after dosing of dasatinib.

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CRITERIA FOR CYTOGENETIC AND HEMATOLOGIC 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

Cytogenetic response[2]

- Complete- No Ph[1]-positive metaphases
- Partial- 1%-34% Ph-positive metaphases
- Minor- 35%-90% Ph-positive metaphases

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

[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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Chronic Myelogenous Leukemia

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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]
• 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	• 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	• 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.	• 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] Jaffe 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

Back to Disease Progression (CML-5)

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Chronic Myelogenous Leukemia

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] Jaffe 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

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

Back to Disease Progression (CML-5)

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Manuscript

NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Chronic myelogenous leukemia (CML) accounts for 15% of adult leukemias. In 2006, an estimated 4,500 cases will be diagnosed, and 900 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)

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% to 80% of patients. Several definitions of the accelerated and blast phase are summarized in the algorithm (CML-G, CML-H).

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. This translocation results in the head-to-tail fusion of the breakpoint cluster region (*bcr*) gene on chromosome 22 at band q11 and the *abl* (named after the Abelson murine leukemia virus) gene 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, $p210^{BCR\text{-}ABL}$; this protein contains NH_2-terminal domains of *bcr* and the COOH-terminal domains of *abl*. Another *bcr-abl* fusion protein, p190, may be produced, but this is almost always in the setting of Philadelphia chromosome-positive (Ph^1-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.

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. Cytogenetic remission, based on the absence of the Philadelphia chromosome (Ph[1]), can be further evaluated by measuring the presence, absence (i.e. qualitative) or number (i.e. quantitative) of *brc-abl* mRNA transcripts using polymerase chain reaction (PCR) techniques. The *bcr-abl* mRNA transcripts typically fall slowly after complete cytogenetic remission is reached. The criteria for cytogenetic and hematologic responses are summarized in CML-E.

Conventional metaphase cytogenetic testing for Ph[1] is widely available, relatively quick, and reliable; however, the sensitivity is approximately 5% if only 20 metaphases are examined. 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 of >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 Ph[1] levels. At this point, more sensitive techniques are required. The most sensitive assay available is reverse transcriptase-polymerase chain reaction (RT-PCR) for the *bcr-abl* chimeric mRNA; this assay can detect one CML cell in a background of ≥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 Ph[1]-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.[4,5] 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.[6-10]

Therefore, QPCR testing plays an important role in monitoring patient response in many CML patients who achieve a cytogenetic remission.[10] 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.[4,5] 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 quantitation of the assay variable. A substantial effort has been made to “harmonize” *bcr-abl* testing and reporting across academic and private laboratories.[10]

Initial Workup (CML-1)

The panel recommended the following tests as part of the initial evaluation of 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 fluorescence in situ hybridization,and PCR (only if a quantitative PCR is available).

Cytogenetic analysis, as well as more sensitive testing (FISH and PCR), is used at baseline to detect the Philadelphia chromosome and/or the *bcr- abl* hybrid (Ph negative, *bcr-abl* positive) as well as for assessing the response to therapy.[11,12]

CML patients with *bcr-abl*-negative disease have a significantly worse prognosis than those with *bcr-abl*-positive disease.[13] 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 either karyotype analysis, FISH or molecular techniques) are the focus of this NCCN guideline.

Primary Treatment

The NCCN guidelines discuss 3 potential primary treatment options for CML: 1. imatinib mesylate; 2. allogeneic hematopoietic stem cell transplantation (HSCT); or (3) clinical trial.

Imatinib mesylate, approved by the FDA in 2001, is a potent and specific inhibitor of the *bcr-abl* tyrosine kinase; this class of drugs has revolutionized the treatment of CML. 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 trial, a trial of 1106 patients 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 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 updated results are now available.[16] With a median follow-up of 54 months, the overall estimated survival was 90%; 84% of patients had not progressed on treatment and 93% of patients were free from progression to either accelerated or blast phase. This data confirms the high durable response rates to imatinib. Based on this data, the panel concluded that interferon-based therapy should no longer be considered as routine initial therapy for CML and at a daily dosage of 400 mg, imatinib is considered a category 1 recommendation for newly diagnosed patients.

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 treated with 400 mg imatinib twice daily; 96% had a major cytogenetic response and 90% (Ph < 35%) had a complete cytogenetic response (Ph 0%).[17] 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.[43] Several ongoing studies are focusing on dose escalation of imatinib in newly diagnosed patients.[18,19] 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. Higher dose imatinib for newly diagnosed patients is considered a 2A recommendation.

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.[20-23] However, further follow-up is clearly warranted in this setting.

Management of hematologic and non-hematologic toxicities caused by imatinib, as well as specific, panel-recommended interventions, are summarized in the algorithm and reported in detail in the recent biomedical literature.[6,14-16] Potential drug interactions with imatinib are also summarized (CML-C). Erythropoietin has been shown to be effective in patients who develop imatinib-associated anemia.[24]

Rare patients unable to tolerate imatinib may be considered for IFN therapy. However, most of the NCCN participating centers believe that interferon should no longer be considered an upfront option for the treatment of CML given the excellent long term results with imatinib. Of patients treated with interferon, 10% to 15% achieve a complete cytogenetic response and have 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. Management of interferon toxicity is discussed in CML-F.

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).[6] 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.[10]

The optimal guidelines for monitoring response to imatinib therapy are detailed in CML-A. 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 after 3 months when the patient is 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 is recommended even without any early evidence of relapse on the basis of FISH or QPCR since chromosomal abnormalities may emerge in Philadelphia negative cells.[25-27]For example, in a case series of 1001 patients treated with imatinib, clonal abnormalities were detected in 34.[28] Another case series reported clonal abnormalities and in 21 of 342 patients.[27] 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 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.

3 and 6-Month Follow-up Therapy in Patients Receiving Imatinib (CML-2)

After three months of imatinib therapy, patients are categorized according to whether or not hematologic remission is present.

Recommended treatment options for patients not in remission or in relapse have been revised since 2006. Interferon with or without cytarabine or dose escalation of imatinib is no longer recommended. These changes are related in part to the availability of dasatinib, which was FDA approved in 2006. Dasatinib 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.[29] The FDA approved labeling states that dasatinib is indicated for the treatment of adults in all phases of CML(chronic, accelerated, or myeloid or lymphoid blast phase) with resistance or intolerance to prior therapy, including imatinib. Results from 4 single arm clinical studies used to support the FDA approval have not been published in the peer reviewed literature, but are summarized in the package insert.[30] These studies focused on patients with all stages of CML who were intolerant of or had disease resistant to imatinib. Resistance 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. Patients received dasatinib 70 mg BID on a continuous basis. The major cytogenetic response rate for chronic, accelerated and blast phase CML was 45%, 31% and 30%, respectively. The package insert notes that while the clinical trials reported hematologic and cytogenetic response rates, there are no controlled trials demonstrating a clinical benefit, such as improvement in disease related symptoms or increased survival. Therefore, dasatinib is considered a category 2A recommendation. Management of dasatinib toxicity is addressed in CML-D. 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 a cytogenetic evaluation; patients are then classified into complete, partial/minor cytogenetic response or no response/relapsed disease. 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 consider switching to dasatinib, allogeneic transplant or participation in a clinical trial.[31] Interferon with or without cytarabine is no longer recommended.

12 and 18 Month Follow for Those Receiving Imatinib (CML-3)

Bone marrow cytogenetics are evaluated again at 12 months, and disease again categorized as complete, partial, 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, and dasatinib, a clinical trial or allogeneic transplant is considered for those with a minor or no cytogenetic response. 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, allogeneic transplant or participation in a clinical trial.

Disease Progression While on Imatinib (CML-5)

Classically disease progression is defined as either progression to accelerated phase or blast crisis. No uniform consensus was reached about the definition of accelerated phase; therefore, 4 different definitions are provided in the guidelines (CML-G).[32-35] 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.[35] The World Health Organization (WHO) criteria for blast crisis have also been incorporated into the algorithm.[35] Treatment of disease progression following imatinib therapy consists of dasatinib, followed by allogeneic transplant, if feasible, or participation in a clinical trial. An ALL-type induction therapy is appropriate for those with a lymphoid blast crisis, while an AML-type induction therapy is appropriate for those with a myeloid blast crisis.

Most patients will achieve a complete cytogenetic remission with imatinib therapy, thus the need for more sensitive monitoring techniques such as QPCR. Once a patient has achieved a complete cytogenetic remission disease progression may also be considered loss of complete cytogenetic response or loss of complete hematologic response. Options at that point include increasing the dose of imatinib, switching to dasatinib, allogeneic transplant, or clinical trial. Resistance 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 allogenic transplant, or placed on a clinical trial of another tyrosine kinase inhibitor, such as nilotinib.[36-41] However, patients who develop a T315I mutation will 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.[38] 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.

Allogeneic Transplant

The excellent results with imatinib have challenged the role of allogeneic transplant as a first line therapy. However, given its proven curative potential, the panel believes that this should still be considered a front-line option for some patients, depending on risk. Nonetheless, the widespread application of 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 molecular 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. 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.[42,43]

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.[44-48]

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.[42,43,49] 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.[42,49] 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.[49,50]

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. [51-53]

Indeed some studies suggested that previous imatinib treatment might lead to increased regimen-related toxicity after transplant, especially liver toxicity,[54,55] while other studies suggested no increase in toxicity.[56,57] Of note is that these studies include very heterogenous 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.[58] There was no significant difference between the two groups regarding death, relapse rate and non-relapse mortality. These data suggest that pretransplant imatinib does not compromise the outcome of a subsequent allogeneic transplant.

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. For chronic phase disease, transplantation can be considered for those who have a poor initial response (i.e., no cytogenetic response at 6 months; no major response by 12 months), or those who relapse after an initial response (especially those with a T315I mutation). Allogeneic transplant is an immediate consideration in patients presenting with accelerated phase or blast crisis CML, although these patients may benefit from a course of imatinib as a "bridge" to transplantation.

In summary the NCCN guidelines suggest that allogeneic transplant can be considered at several points during the disease course of CML as follows:

- As initial therapy in newly diagnosed patients, though at the present time, most patients are initially treated with imatinib therapy. (CML-1)
- In patients who do not achieve hematologic remission after three months of imatinib therapy. (CML-2)
- In patients with a hematologic remission after 3 months of imatinib therapy, but who do not have a cytogenetic response after 6-12 months of imatinib therapy (CML-2)
- In patients on imatinib with accelerated phase disease or blast crisis. (CML-5)

CML-4 focuses on follow-up for patients receiving allogeneic transplant as primary therapy. Patients are categorized into those with or without cytogenetic remission, and those in cytogenetic remission are further evaluated with a qualitative PCR test to determine the presence or absence of *bcr-abl*. 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.[4,5,59,60] For patients who relapse after transplantation, donor lymphocyte infusions (DLI) or interferon are effective in inducing remissions, though they are more effective in chronic phase than advanced phase.[61,62] Moreover, DLI administration is precluded by active GVHD. More recently imatinib has been administered for hematologic, cytogenetic, and molecular relapse, and has been shown to very effective in inducing remissions, particularly in patients with chronic phase disease, in molecular or cytogenetic relapse.[63,64] Prophylactic imatinib therapy early post-transplant for high risk Ph+ leukemia is currently being studied in clinical trials.

Thus, patients who relapse can first be categorized according to the presence or absence of GVHD. Those with GVHD may be treated with imatinib or participate in a clinical trial. Interferon is no longer a recommended treatment option for these patients. 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. DLI can be considered in these patients. Patients who do not achieve a complete cytogenetic response after immunosuppression can be treated with imatinib, interferon, donor leukocyte infusion or participate in a clinical trial.[65] It is recommended that patients who relapse in the presence of GVHD should receive imatinib or go on a clinical trial.

Patients who do achieve cytogenetic remission after allogeneic transplant are followed with PCR monitoring. 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.

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