Overview
Chronic myelogenous leukemia (CML) accounts for 15% of adult leukemias. Although the median age of disease onset is 67 years, CML occurs in all age groups (Surveillance, Epidemiology, and End Results [SEER] statistics). In 2009, an estimated 5050 cases will be diagnosed and 470 patients will die from the disease in the United States.1

CML is a hematopoietic stem cell disease, which is characterized by a reciprocal translocation between chromosomes 9 and 22, resulting in the formation of the Philadelphia chromosome (Ph chromosome). This translocation t(9;22) results in the head-to-tail fusion of the breakpoint cluster region (BCR) gene on chromosome 22 at band q11 and the Abelson murine leukemia (ABL) gene located...
Chronic Myelogenous Leukemia

The BCR-ABL gene encodes a protein (p210BCR-ABL), with deregulated tyrosine kinase activity. This protein contains NH₂-terminal domains of BCR and the COOH-terminal domains of ABL. Another fusion protein, p190, may be produced, but it is usually in the setting of Ph+ 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 p210BCR-ABL promote the transition from a benign to a malignant state are not entirely understood. However, attachment of the BCR sequences to ABL results in 3 critical functional changes: 1) the abl protein becomes constitutively active as a protein tyrosine kinase enzyme, 2) the DNA protein-binding activity of abl is attenuated, and 3) the binding of abl to cytoskeletal actin microfilaments is enhanced. These effects increase proliferation, affect differentiation, and block apoptosis.

CML occurs in 3 different phases (chronic, accelerated, and blast phase), but is usually diagnosed in the chronic phase. However, gene expression profiling has shown a close correlation of gene expressions between the accelerated phase and blast crisis. The bulk of the genetic changes in progression occur during transition from chronic to accelerated phase.

The activation of beta-catenin–signaling pathway in CML granulocyte-macrophage progenitors (which

**NCCN Chronic Myelogenous Leukemia Panel Members**

*Susan O’Brien, MD/Chair†
  University of Texas M. D. Anderson Cancer Center
Ellin Berman, MD††
  Memorial Sloan-Kettering Cancer Center
Hossein Borghaei, DO, MS††
  Fox Chase Cancer Center
*Daniel J. DeAngelo, MD, PhD††
  Dana-Farber/Brigham and Women’s Cancer Center
Marcel P. Devetten, MD†‡
  UNMC Eppley Cancer Center at The Nebraska Medical Center
Steven Devine, MD†
  The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute
Harry P. Erba, MD, PhD††
  University of Michigan Comprehensive Cancer Center
*Jason Gotlib, MD, MS‡
  Stanford Comprehensive Cancer Center
Madan Jagasia, MD‡
  Vanderbilt-Ingram Cancer Center
Joseph O. Moore, MD†
  Duke Comprehensive Cancer Center
*Tariq Mughal, MD††
  St. Jude Children’s Research Hospital/
  University of Tennessee Cancer Institute
Javier Pinilla-Ibarz, MD, PhD†
  H. Lee Moffitt Cancer Center & Research Institute
*Jerald P. Radich, MDξ
  Fred Hutchinson Cancer Research Center/
  Seattle Cancer Care Alliance
*Neil P. Shah, MD, PhD‡
  UCSF Helen Diller Family Comprehensive Cancer Center
*Paul J. Shami, MD‡
  Huntsman Cancer Institute at the University of Utah
B. Douglas Smith, MD†Þ
  The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
*David S. Snyder, MD†ζ
  City of Hope Comprehensive Cancer Center
Martin S. Tallman, MD†
  Robert H. Lurie Comprehensive Cancer Center of Northwestern University
Moshe Talpaz, MD†
  University of Michigan Comprehensive Cancer Center
*Meir Wetzler, MD†Þ
  Roswell Park Cancer Institute

**KEY:**

* Writing Committee Member

Specialties: †Hematology/Hematology Oncology; ‡Medical Oncology; ξBone Marrow Transplantation
WORKUP\(^a\)

Chronic phase adult CML

- H&P
- CBC, platelets
- Chemistry profile
- Consider HLA testing
- Bone marrow aspirate and biopsy\(^b\)
  - Morphologic review
    - Percent blasts
    - Percent basophils
  - Cytogenetics, FISH,\(^c\) QPCR

Ph\(^1\) negative and BCR-ABL negative
  \[\rightarrow\]
  Evaluate for other diseases (not CML)

Ph\(^1\) positive or BCR-ABL positive
  \[\rightarrow\]
  Discussion of treatment options\(^d,e\)
  - Imatinib
  - Role of HSCT\(^f,g\)
  - Clinical trial

\(^a\)See Monitoring for Patients Receiving Tyrosine Kinase Inhibitor therapy (page 992).
\(^b\)Bone marrow is preferable for the initial workup, not only to provide morphologic review, but also to detect chromosomal abnormalities that are not detectable on peripheral blood FISH.
\(^c\)See text for further discussion regarding the role of FISH in the initial workup of patients with CML.
\(^d\)There is 7 year follow-up data which shows clear evidence of excellent survival benefit with imatinib. See text for additional information.
\(^e\)For patients with symptomatic leukocytosis or thrombocytosis, see Supportive Care Strategies (page 992).
\(^f\)HSCT = hematopoietic stem cell transplantation. Refers to a matched related and unrelated allogeneic transplant. HLA testing should be performed if considering HSCT.
\(^g\)Indications and outcomes of related and unrelated transplant are age, donor type, and transplant center dependent. Nonmyeloablative transplant is under investigation and should be performed only in the context of a clinical trial.
\(^h\)There are data suggesting a faster time to MMR with a higher dose of imatinib but whether this is an important end point in long-term outcome is unknown. Cortes J, Baccarani M, Guilhot F, et al. A phase III, randomized, open-label study of 400 mg versus 800 mg of imatinib mesylate in patients with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase using molecular endpoints: 1 year results of TOPS study [abstract]. Blood 2006;112:Abstract 335.
\(^i\)See Management of Imatinib Toxicity (page 993).
\(^j\)Rare patients unable to tolerate imatinib, dasatinib, or nilotinib should consider IFN/PEG-IFN or clinical trial.
**Chronic Myelogenous Leukemia Version 2:2010**

### 3 MONTH FOLLOW-UP THERAPY

- **Hematologic remission**
  - Continue same dose of imatinib

- **Not in hematologic remission or hematologic relapse**
  - 3-month evaluation
  - Evaluate patient compliance and drug-drug interactions
  - Consider mutational analysis

### 6 MONTH FOLLOW-UP THERAPY

- **Complete cytogenetic response or partial response**
  - 6-month evaluation including bone marrow cytogenetics

- **Minor cytogenetic response**
  - Continue same dose of imatinib

- **No cytogenetic response**
  - Evaluate patient compliance and drug-drug interactions
  - Consider mutational analysis

- **Complete cytogenetic response or partial response**
  - Continue same dose of imatinib

### Discussion of treatment options
- **Imatinib**
- **Role of HSCT**
- **Clinical trial**

### 3-MONTH FOLLOW-UP THERAPY

- **Complete cytogenetic response or partial response**
  - Continue same dose of imatinib

- **Minor cytogenetic response**
  - Continue same dose of imatinib or increase dose of imatinib to a maximum of 800 mg, as tolerated

- **No cytogenetic response**
  - Evaluate patient compliance and drug-drug interactions
  - Consider mutational analysis

### 6-MONTH FOLLOW-UP THERAPY

- **Complete cytogenetic response or partial response**
  - Continue same dose of imatinib

- **Minor cytogenetic response**
  - Continue same dose of imatinib or increase dose of imatinib to a maximum of 800 mg, as tolerated

- **No cytogenetic response**
  - Evaluate patient compliance and drug-drug interactions
  - Consider mutational analysis

### 12-MONTH FOLLOW-UP THERAPY

- **Complete cytogenetic response or partial response**
  - Continue same dose of imatinib

- **Minor cytogenetic response**
  - Continue same dose of imatinib or increase dose of imatinib to a maximum of 800 mg, as tolerated

- **No cytogenetic response**
  - Evaluate patient compliance and drug-drug interactions
  - Consider mutational analysis

### Criteria for Cytogenetic, Hematologic, and Molecular Response

- See Monitoring for Patients Receiving Tyrosine Kinase Inhibitor therapy (page 992).
- HSCT = hematopoietic stem cell transplantation. Refers to a matched related and unrelated allogeneic transplant. HLA testing should be performed if considering HSCT.
- See Management of Imatinib Toxicity and Drug Interactions (pages 993-995).
- Rare patients unable to tolerate imatinib, dasatinib, or nilotinib should consider IFN/PEG-IFN or clinical trial.
- See Criteria for Cytogenetic, Hematologic, and Molecular Response (page 996).
- See Management of Dasatinib Toxicity and Drug Interactions (pages 996 and 997).
- See Management of Nilotinib Toxicity and Drug Interactions (pages 997 and 998).
- See Important Considerations with Nilotinib (page 998).
12-MONTH FOLLOW-UP THERAPY*

- **Complete cytogenetic response**
  - Continue same dose of imatinib
  - See 18-Month Follow-up Therapy (facing page)

- **Partial cytogenetic response**
  - Continue same dose of imatinib
  - Increase dose of imatinib to a maximum of 800 mg, as tolerated

- **Minor or no cytogenetic response**
  - Evaluate patient compliance and drug-drug interactions
  - Consider mutational analysis

- **Cytogenetic relapse**
  - Dasatinib
  - Nilotinib
  - Increase dose of imatinib to a maximum of 800 mg
  - Evaluate for HSCT depending on response to secondary therapy (see page 990) or Clinical trial

---

*See Monitoring for Patients Receiving Tyrosine Kinase Inhibitor therapy (page 992).

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

2 See Management of Imatinib Toxicity and Drug Interactions (pages 993-995).

3 Rare patients unable to tolerate imatinib, dasatinib, or nilotinib should consider IFN/PEG-IFN or clinical trial.

4 See Criteria for Cytogenetic, Hematologic, and Molecular Response (page 996).

5 See Management of Dasatinib Toxicity and Drug Interactions (pages 996 and 997).

6 See Management of Nilotinib Toxicity and Drug Interactions (pages 997 and 998).

7 See Important Considerations with Nilotinib (page 998).

8 Therapy should continue indefinitely and not be discontinued.
18-MONTH FOLLOW-UP THERAPY

- **Complete cytogenetic response**
  - Continue same dose of imatinib
  - See Disease Progression (page 991)

- **18-month evaluation including bone marrow cytogenetics**
  - Partial cytogenetic relapse or cytogenetic relapse
    - Dasatinib or Nilotinib
    - Increase dose of imatinib to a maximum of 800 mg, as tolerated
    - Evaluate for HSCT depending on response to secondary therapy (see page 990) or Clinical Trial

- **Minor or no cytogenetic response**
  - Evaluate patient compliance and drug-drug interactions
  - Consider mutational analysis
  - Dasatinib or Nilotinib
  - Evaluate for HSCT depending on response to secondary therapy (see page 990) or Clinical Trial

---

See Monitoring for Patients Receiving Tyrosine Kinase Inhibitor therapy (page 992).

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

i See Management of Imatinib Toxicity and Drug Interactions (pages 993-995).

j Rare patients unable to tolerate imatinib, dasatinib, or nilotinib should consider IFN/PEG-IFN or clinical trial.

k See Criteria for Cytogenetic, Hematologic, and Molecular Response (page 996).

l See Management of Dasatinib Toxicity and Drug Interactions (pages 996 and 997).

m See Management of Nilotinib Toxicity and Drug Interactions (pages 997 and 998).

n See Important Considerations with Nilotinib (page 998).

o Therapy should continue indefinitely and not be discontinued.
**FOLLOW-UP THERAPY**

**Cytogenetic remission**

- **Positive**
  - QPCR monitoring (peripheral blood) every 3 months for 2 years, then 6 months for 3 years
  - Discuss options with transplant team: imatinib, dasatinib, nilotinib or DLI or IFN/PEG-IFN or Clinical trial

- **Negative**
  - Monitored withdrawal of immune suppression
  - Discuss options with transplant team: imatinib, dasatinib, nilotinib or DLI or IFN/PEG-IFN or Clinical trial

**HSCT**

- Not in remission, or in relapse

1. HSCT = hematopoietic stem cell transplantation. Refers to a matched related and unrelated allogeneic transplant. HLA testing should be performed if considering HSCT.
2. 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.
3. See Management of Imatinib Toxicity (page 993).
4. See Criteria for Cytogenetic, Hematologic, and Molecular Response (page 996).
5. See Management of Dasatinib Toxicity and Drug Interactions (pages 996 and 997).
6. See Management of Nilotinib Toxicity and Drug Interactions (pages 997 and 998).
7. See Important Considerations with Nilotinib (page 998).
8. There are data for imatinib posttransplant, but not in patients who have previously failed imatinib. Other TKIs may be more appropriate although there are no published data to support their use posttransplant.
9. See Management of IFN Toxicity (page 999).
**WORKUP**

- **Accelerated phase**
- **Disease progression on imatinib**
- **Blast crisis**

**TREATMENT**

- **Dasatinib** or **nilotinib** followed by **HSCT**, if feasible or clinical trial
- **ALL-type induction chemotherapy + dasatinib**, followed by **HSCT**, if feasible or clinical trial
- **AML-type induction chemotherapy + dasatinib**, followed by **HSCT**, if feasible or clinical trial

---

**To view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org.**

---

1. **HSCT** = hematopoietic stem cell transplantation. Refers to a matched related and unrelated allogeneic transplant. HLA testing should be performed if considering HSCT.
2. See Management of Dasatinib Toxicity (page 996).
3. See Management of Nilotinib Toxicity (page 997).
4. See Important Considerations with Nilotinib (page 998).
5. See Definitions of Accelerated Phase (page 1000).
6. See Definitions of Blast Crisis (page 1001).
7. Patients presenting with de novo Ph+ acute leukemia or de novo accelerated or blast phase should be considered for combination chemotherapy + TKI (imatinib or dasatinib) or clinical trial.
MONITORING FOR PATIENTS RECEIVING TYROSINE KINASE INHIBITOR THERAPY

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 bone marrow 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 months, it is not necessary to repeat bone marrow cytogenetics at 12 months.
- 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 months.
- 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.

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, anti-aggregants, anagrelide, or apheresis

---

MANAGEMENT OF IMATINIB TOXICITY

**Hematologic**
- Grade 3-4 neutropenia (absolute neutrophil count [ANC] < 1000/mm³): hold drug until ANC ≥ 1500/mm³, then resume imatinib at the starting dose of 400 mg. If recurrence of ANC < 1000/mm³, hold drug until ANC ≥ 1500/mm³, then resume imatinib at reduced dose of 300 mg.
- Grade 3-4 thrombocytopenia (platelet count < 50,000/mm³): hold drug until platelet count ≥ 75,000/mm³, then resume imatinib at the starting dose of 400 mg. If recurrence of platelet count < 50,000/mm³, hold drug until platelet count ≥ 75,000/mm³, then resume imatinib at reduced dose of 300 mg.
- In accelerated and blast phases, patients may have cytopenias related to disease. If cytopenia is unrelated to disease, reduce dose to 400 mg. If cytopenia persists 2 weeks, reduce dose further to 300 mg. If cytopenia persists for 4 weeks, stop imatinib until ANC ≥ 1000/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.
- Grade 3-4 anemia.

**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 left ventricular ejection fraction.
- 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 < 300 mg). Consider change to dasatinib, nilotinib, or clinical trial.

**Potential Drug Interactions**

1. Information from FDA label, available at www.fda.gov.
2. Many toxicities are self-limiting, consider re-escalating dose at a later time.
4. Although erythropoietin is effective, recent guidelines from the Centers for Medicaid and Medicare Services (CMS) and the FDA do not support the use of erythropoietic stimulating agents (ESAs) in myeloid malignancies.
### POTENTIAL DRUG INTERACTIONS WITH IMATINIB

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INTERACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Imatinib can cause LFT abnormalities. Liver failure and death occurred in 1 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 acetaminophen, ≤ 1300 mg/d.</td>
</tr>
<tr>
<td>Aprepitant</td>
<td>Aprepitant inhibits CYP450 3A4, increasing the imatinib plasma concentration.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Carbamazepine induces CYP450 3A4 and decreases the plasma concentration of imatinib. Increase in imatinib dose is usually necessary.</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Clarithromycin inhibits CYP450 3A4, increasing the imatinib plasma concentration.</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Imatinib inhibits CYP450 3A4, increasing the cyclosporine plasma concentration; this is a concern given the narrow therapeutic window of cyclosporine.</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Dexamethasone induces CYP450 3A4, decreasing the imatinib plasma concentration. Increase in imatinib dose is usually necessary.</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Erythromycin inhibits CYP450 3A4, increasing the imatinib plasma concentration.</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>Grapefruit juice may increase plasma concentrations of imatinib and should be avoided.</td>
</tr>
<tr>
<td>Hypericum perforatum</td>
<td>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.</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Itraconazole inhibits CYP450 3A4, increasing the imatinib plasma concentration.</td>
</tr>
</tbody>
</table>

Abbreviations: CYP450, cytochrome P450; LFT, liver function test.

Potential Drug Interactions continued (see facing page)

---

### POTENTIAL DRUG INTERACTIONS WITH IMATINIB

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INTERACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>Ketoconazole inhibits CYP450 3A4, increasing the imatinib plasma concentration.</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Phenobarbital induces CYP450 3A4, decreasing the imatinib plasma concentration. Increase in imatinib dose is usually necessary.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Phenytoin induces CYP450 3A4, decreasing the imatinib plasma concentration. Increase in imatinib dose is usually necessary.</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Imatinib inhibits CYP450 3A4, increasing pimozide plasma concentration. This is a concern given the narrow therapeutic window of pimozide.</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Rifabutin induces CYP450 3A4, decreasing the imatinib plasma concentration. Increase in imatinib dose is usually necessary.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Rifampin induces CYP450 3A4, decreasing the imatinib plasma concentration. Increase in imatinib dose is usually necessary.</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>Rifapentine induces CYP450 3A4, decreasing the imatinib plasma concentration. Increase in imatinib dose is usually necessary.</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Imatinib inhibits CYP450 3A4, increasing the simvastatin plasma concentration. A dose adjustment of simvastatin may be necessary.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>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.</td>
</tr>
</tbody>
</table>

Abbreviations: CYP450, cytochrome P450; LFT, liver function test

---

MANAGEMENT OF DASATINIB TOXICITY

**Hematologic**
- Grade 3-4 neutropenia (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 and blast phases, 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 180 mg daily.
- Growth factors can be used in combination with dasatinib for patients with resistant neutropenia and thrombocytopenia.
- Grade 3-4 anemia.

**Specific Interventions**
- Fluid retention events (ascites, edema, pleural and pericardial effusion) are managed with diuretics, supportive care.
- Pleural/pericardial effusion: diuretics, dose interruption. If patient has significant symptoms, consider short course of steroids (prednisone, 20 mg/d 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, and then consider resuming at reduced dose level depending on the severity of the initial event or change to nilotinib.

**POTENTIAL DRUG INTERACTIONS WITH DASATINIB**

1. **H2 Blockers/Proton Pump Inhibitors:**
   - Famotidine, omeprazole is likely to reduce dasatinib exposure. The concomitant use of H2 blockers or proton pump inhibitors with dasatinib may increase plasma concentrations of dasatinib and should be avoided.

2. **Antacids:**
   - Simultaneous administration of dasatinib with antacids (e.g., aluminum hydroxide, magnesium hydroxide) is likely to reduce dasatinib exposure. The concomitant use of H2 blockers or proton pump inhibitors with dasatinib may increase plasma concentrations of dasatinib and should be avoided.

3. **Nonclinical data show that the solubility of dasatinib is pH-dependent. Simultaneous administration of dasatinib with antacids may increase plasma concentrations of dasatinib and should be avoided.**

4. **Drug-drug interactions with dasatinib**
   - **CYP3A4 inhibitors:**
     - Antacids: hold drug until serum levels return to baseline. If QTcF is between 450 and 480 ms after 2 weeks, resume at reduced dose (400 mg, once a day). After dose reduction, if QTcF > 480 ms: hold drug if serum potassium and magnesium levels are below lower limit of normal; correct with electrolytes.
     - **H2 Blockers/Proton Pump Inhibitors:**
       - Hold drug if serum potassium and magnesium levels are below lower limit of normal; correct with electrolytes.
     - **Drugs that may have their plasma concentration altered by dasatinib:**
       - **Antacids:**
         - Hold drug if serum potassium and magnesium levels are below lower limit of normal; correct with electrolytes.
       - **CYP3A4 inhibitors:**
         - Hold drug if serum potassium and magnesium levels are below lower limit of normal; correct with electrolytes.

5. **Hypericum perforatum (St. John’s wort) may decrease dasatinib plasma concentrations unpredictably. Patients receiving St. John’s wort must be carefully monitored for toxicity.**

6. **Other drugs that may have their plasma concentration altered by dasatinib:**
   - **Drugs that are less affected by dasatinib:**
     - **Antacids:**
       - Hold drug if serum potassium and magnesium levels are below lower limit of normal; correct with electrolytes.
     - **CYP3A4 inhibitors:**
       - Hold drug if serum potassium and magnesium levels are below lower limit of normal; correct with electrolytes.

7. **Drugs that may have their plasma concentration altered by dasatinib:**
   - **Antacids:**
     - Hold drug if serum potassium and magnesium levels are below lower limit of normal; correct with electrolytes.
   - **CYP3A4 inhibitors:**
     - Hold drug if serum potassium and magnesium levels are below lower limit of normal; correct with electrolytes.

8. **Other drugs that may have their plasma concentration altered by dasatinib:**
   - **Antacids:**
     - Hold drug if serum potassium and magnesium levels are below lower limit of normal; correct with electrolytes.
   - **CYP3A4 inhibitors:**
     - Hold drug if serum potassium and magnesium levels are below lower limit of normal; correct with electrolytes.

9. **Other drugs that may have their plasma concentration altered by dasatinib:**
   - **Antacids:**
     - Hold drug if serum potassium and magnesium levels are below lower limit of normal; correct with electrolytes.
   - **CYP3A4 inhibitors:**
     - Hold drug if serum potassium and magnesium levels are below lower limit of normal; correct with electrolytes.

10. **Other drugs that may have their plasma concentration altered by dasatinib:**
    - **Antacids:**
      - Hold drug if serum potassium and magnesium levels are below lower limit of normal; correct with electrolytes.
    - **CYP3A4 inhibitors:**
      - Hold drug if serum potassium and magnesium levels are below lower limit of normal; correct with electrolytes.

**CRITERIA FOR CYTOGENETIC, HEMATOLOGIC, AND MOLECULAR RESPONSE**

**Cytogenetic Response**
- Complete: No Ph1-positive metaphases
- Major: 0%-35% Ph-positive metaphases (complete + partial)
- Partial: 36%-39% Ph-positive metaphases
- Minor: 40%-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

**CRITERIA FOR CYTOKINETIC, HEMATOLOGIC, AND MOLECULAR RESPONSE**


2. A minimum of 20 metaphases should be examined.


4. Although erythropoietin is effective, recent guidelines from CMS and the FDA do not support the use of ESAs in myeloid malignancies.
Chronic Myelogenous Leukemia Version 2:2010

POTENTIAL DRUG INTERACTIONS WITH DASATINIB

Drugs that may Increase Dasatinib Plasma Concentrations
CYP3A4 Inhibitors: Dasatinib is a CYP3A4 substrate. Concomitant use of dasatinib and drugs that inhibit CYP3A4 (e.g., ketoconazole,itraconazole, erythromycin, clarithromycin, ritonavir, atazanavir, indinavir, nefazodone, neflnavir, saquinavir, telithromycin) may increase exposure to dasatinib and should be avoided. Patients treated with dasatinib should be closely monitored 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. For patients in whom CYP3A4 inducers (e.g., 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 show 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 before 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 (e.g., famotidine, omeprazole) is likely to reduce dasatinib exposure. The concomitant use of H2 blockers or proton pump inhibitors with dasatinib is not recommended. Antacids should be considered in place of H2 blockers or proton pump inhibitors in patients undergoing 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, amitriptyline, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, platelet glycoprotein IIb/IIIa inhibitors, and ergot alkaloids (e.g., ergotamine, dihydroergotamine) should be administered with caution in patients receiving dasatinib. Grapefruit juice may increase plasma concentrations of dasatinib and should be avoided.

MANAGEMENT OF NILOTINIB TOXICITY

QT Interval Prolongation
- ECGs with a QTC > 480 ms: 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 < 450 msec and within 20 ms of baseline. If QTCf is between 450 and 480 ms after 2 weeks, resume at reduced dose (400 mg, once a day). After dose reduction, if QTCf returns to > 480 ms, nilotinib should be discontinued. ECG should be obtained 7 days after any dose adjustment to monitor QTC.

Hematologic
- Grade 3-4 neutropenia (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 conjunction with nilotinib for patients with resistant neutropenia and thrombocytopenia.
- Grade 3-4 anemia.²

Specific Interventions
- Headache: supportive care.
- Nausea: supportive care.
- Diarrhea: supportive care.
- Rash: topical or systemic steroids, dose reduction, interruption, or discontinuation.

Nonhematologic
- Grade 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 CMS and the FDA do not support the use of ESAs in myeloid malignancies
POTENTIAL DRUG INTERACTIONS WITH NILOTINIB

Drugs that may Increase Nilotinib Plasma Concentrations

**CYP3A4 Inhibitors:** Nilotinib is a competitive inhibitor of CYP3A4. Concomitant administration of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nefinavir, 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 the 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 coadministered with PgP inhibitors.

**CYP3A4 Inducers:** Drugs that induce CYP3A4 activity may decrease nilotinib plasma concentrations. The concomitant use of strong CYP3A4 inducers (e.g., 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 level of tolerance. Nilotinib dose should be reduced to the indicated dose after discontinuation of CYP3A4 inducers.

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 (e.g., 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 level of tolerance. Nilotinib dose should be reduced to the indicated dose after 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, thereby decreasing the concentrations of drugs that 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.

IMPORTANT CONSIDERATIONS WITH NILOTINIB

- Nilotinib prolongs the QT interval. Sudden deaths have been reported in patients receiving nilotinib.
- Nilotinib should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected before nilotinib administration and should be periodically monitored.
- Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided.
- Patients should avoid food 2 hours before and 1 hour after taking dose.
- Nilotinib should be used with caution in patients with hepatic impairment.
- ECGs should be obtained to monitor the QTc at baseline, 7 days after initiation, and periodically thereafter, and after any dose adjustments.

1Information from FDA label, available at www.fda.gov
## MANAGEMENT OF INTERFERON TOXICITY

### Management:
- Depression: antidepressants (e.g., fluoxetine, paroxetine)
- Thyroid function: monitor every 6 months if marked fatigue
- Pulmonary function: 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 that does not respond to dose reduction
### DEFINITIONS OF ACCELERATED PHASE

<table>
<thead>
<tr>
<th>Criteria of Sokal et al.</th>
<th>International Bone Marrow Transplant Registry Criteria</th>
<th>Criteria Used at M. D. Anderson Cancer Center</th>
<th>WHO Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral blood or marrow blasts ≥ 5%</td>
<td>Leukocyte count difficult to control with hydroxyurea or busulfan</td>
<td>Peripheral blood blasts ≥ 15%</td>
<td>Blasts 10%-19% of WBCs in peripheral and/or nucleated bone marrow cells</td>
</tr>
<tr>
<td>Basophils &gt; 20%</td>
<td>Rapid leukocyte doubling time (&lt; 5 days)</td>
<td>Peripheral blood blasts and promyelocytes ≥ 30%</td>
<td>Peripheral blood basophils ≥ 20%</td>
</tr>
<tr>
<td>Platelet count ≥ 1000 x 10^9/L despite adequate therapy</td>
<td>Peripheral blood or marrow blasts ≥ 10%</td>
<td>Peripheral blood basophils ≥ 20%</td>
<td>Persistent thrombocytopenia (&lt; 100 x 10^9/L) unrelated to therapy, or persistent thrombocytosis (&gt; 1000 x 10^9/L) unresponsive to therapy</td>
</tr>
<tr>
<td>Frequent Pelger-Huet-like neutrophils, nucleated erythrocytes, megakaryocyte nuclear fragments</td>
<td>Peripheral blood or marrow blasts and promyelocytes ≥ 20%</td>
<td>Platelet count ≤ 100 x 10^9/L unrelated to therapy</td>
<td>Persistent thrombocytosis</td>
</tr>
<tr>
<td>Marrow collagen fibrosis</td>
<td>Peripheral blood basophils and eosinophils ≥ 20%</td>
<td>Clonal evolution</td>
<td>Cytogenetic evidence of clonal evolution</td>
</tr>
<tr>
<td>Anemia or thrombocytopenia unrelated to therapy</td>
<td>Anemia or thrombocytopenia unresponsive to hydroxyurea or busulfan</td>
<td>Leukocyte doubling time &lt; 5 days</td>
<td></td>
</tr>
<tr>
<td>Progressive splenomegaly</td>
<td>Persistent thrombocytosis</td>
<td>Increasing spleen size and increasing WBC count unresponsive to therapy</td>
<td></td>
</tr>
<tr>
<td>Leukocyte doubling time &lt; 5 days</td>
<td>Clonal evolution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever of unknown origin</td>
<td>Progressive splenomegaly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Development of myelofibrosis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DEFINITIONS OF ACCELERATED PHASE

Criteria of Sokal et al. 1

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

International Bone Marrow Transplant Registry Criteria 2

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

Criteria Used at M. D. Anderson Cancer Center 3

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

WHO Criteria 4

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

DEFINITIONS OF BLAST CRISIS

WHO Criteria 1

• Blasts ≥ 20% of peripheral blood white cells or nucleated bone marrow cells
• Extramedullary blast proliferation
• Large foci or clusters of blasts in the bone marrow biopsy

International Bone Marrow Transplant Registry 2

• ≥ 30% blasts in the blood, marrow, or both
• Extramedullary infiltrates of leukemic cells

Chronic Myelogenous Leukemia

Text continued from p. 985

enhances the self-renewal activity and leukemic potential of these cells) may also be a key pathobiologic event in evolution to blast crisis CML.\textsuperscript{4} Untreated chronic-phase CML will eventually progress to advanced-phase disease in 3 to 5 years.\textsuperscript{5}

These guidelines discuss the clinical management of chronic and advanced phases of CML and monitoring response to treatment.

**Tyrosine Kinase Inhibitor Therapy**

**Imatinib Mesylate**

Imatinib mesylate (formerly known as STI-571) is a selective inhibitor of the bcr-abl tyrosine kinase.\textsuperscript{6,7} Initial trials with imatinib showed a marked effect as second-line therapy in patients in chronic phase for whom interferon therapy failed or those with more advanced-stage disease (accelerated phase or blast crisis).\textsuperscript{8} At 5-year follow-up, complete cytogenetic response (CCyR) was seen in 41% of patients, and 44% remained on imatinib. At 6-years, estimated rates of freedom from progression (FFP) to accelerated or blast phase and overall survival were 61% and 76%, respectively.\textsuperscript{9}

Patients with newly diagnosed CML were evaluated in the IRIS (International Randomized Study of Interferon and ST1571) trial. This trial randomized 1106 patients to undergo initial therapy with either daily imatinib, 400 mg, or interferon-alpha plus low-dose cytarabine.\textsuperscript{10} Crossover was allowed for patients experiencing treatment failure or intolerance. With a median follow-up of 19 months, the major cytogenetic response (MCyR) rate at 18 months was 87.1% in the imatinib group versus 34.7% in the control group. The estimated rate of CCyR was 76.2% with imatinib and 14.5% with interferon (P < .001). The estimated rate of FFP 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 combination interferon and cytarabine.

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

Long-term follow-up data of the IRIS trial are now available.\textsuperscript{11,12} With a median follow-up of 60 months, estimated cumulative rates of CCyR among patients receiving imatinib were 69% at 12 months and 87% at 60 months. Only 7% of patients had progressed to accelerated-phase CML or blast crisis. The overall survival rate at 60 months was 89% for patients who received imatinib as initial treatment.\textsuperscript{11} These data confirm the high durable response rates with imatinib in a large proportion of patients.

However, because of the high rate of crossover (90%) from interferon-alpha to imatinib mesylate within a year of study, the IRIS trial could not show survival benefit for imatinib mesylate versus interferon. In historical comparisons, survival benefit was significantly better for imatinib than interferon.\textsuperscript{13,14} Estimated 7-year event-free survival (EFS), FFP to accelerated or blast phase, and overall survival were 81%, 93%, and 86%, respectively.\textsuperscript{12} The best observed rates for MCyR and CCyR were 89% and 82%, respectively. The major molecular response (MMR) rate was 85% to 90% at 5 to 6 years for patients experiencing continued response to imatinib. These results show that continuous treatment of chronic-phase CML with imatinib induces durable responses in a large proportion of patients with a decreasing rate of relapse.

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.\textsuperscript{15} Hypophosphatemia, with associated changes in bone and mineral metabolism, has been noted in a small group of patients.\textsuperscript{16} The algorithm summarizes hematologic and nonhematologic toxicities caused by imatinib, and specific, panel-recommended interventions. Erythropoietin and filgrastim have been shown to be effective in patients who develop imatinib-induced anemia and neutropenia, respectively.\textsuperscript{17,18} However, recent guidelines from the Centers for Medicare & Medicaid Services and the FDA do not support the use of erythropoietic stimulating agents in myeloid malignancies. Management of imatinib toxicities are summarized on pages 993 through 995.

**Cardiotoxicity:** In a recent trial, long-term imatinib treatment was associated with congestive heart failure (CHF) and cardiotoxicity.\textsuperscript{19} However, this adverse effect seems to be rare, as shown by the recent
analysis of 1276 patients treated with imatinib at M. D. Anderson Cancer Center. After a median follow-up of 47 months, 22 (1.7%) patients were found to have CHF during imatinib therapy. Of these patients, 13 had undergone prior treatment with cardiotoxic drugs. The authors concluded that CHF is uncommon among patients receiving imatinib, and that its incidence rates are similar to those occurring in the general population. Patients with previous cardiac history should be monitored carefully. Aggressive medical therapy is recommended for symptomatic patients.

Dasatinib
Dasatinib (formerly known as BMS-354825) is a potent, orally available abl kinase inhibitor, similar to imatinib but with the added advantage in that it can bind to both the active and inactive conformation of the abl kinase domain. As a result, dasatinib is active against nearly all imatinib-resistant BCR-ABL mutations in vitro. In a phase I dose-escalation study, dasatinib induced hematologic and cytogenetic responses in patients with CML or Ph-positive ALL who could not tolerate or were resistant to imatinib. 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 experience a complete hematologic response (CHR) within 3 to 6 months, the absence of a MCyR by month 12, or progression of disease after prior response. Dasatinib, 70 mg, was administered twice daily on a continuous basis. Interruption of treatment and dose modifications were allowed for the management of disease progression or toxicity after one treatment cycle.

In the START-C trial, patients with imatinib-resistant or -intolerant chronic-phase CML were treated with dasatinib (70 mg twice daily). An initial result of this study for 186 patients showed that CHR was observed in 90% of patients. Dasatinib also induced MCyR in 52% of the patients; only 2% experienced progression or died after MCyR.

After an 8-month follow-up, the progression-free survival rate was 92%. Extended 2-year follow-up data confirmed that dasatinib induces durable cytogenetic responses in patients with chronic phase CML. After a 24-month follow-up, CHR, MCyR, CCyR, and MMR were observed in 91%, 62%, 53%, and 47% of patients, respectively. Overall and progression-free survival rates at 24 months were 94% and 80%, respectively.

Follow-up data reported by Baccarani et al. confirm the durability of cytogenetic responses with dasatinib. At 2 years follow-up, median time to MCyR and CCyR was 2.9 and 5.5 months, respectively, for patients whose CML was resistant to imatinib. Among patients intolerant to imatinib, median times to achieve MCyR and CCyR were both 2.8 months. Most patients with imatinib-resistant (84% for MCyR and 86% for CCyR) and imatinib-intolerant CML (97% for MCyR and 98% for CCyR) maintained their responses at 24 months.

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

Kantarjian et al. recently reported that once-daily dosing of dasatinib at 140 mg has similar efficacy to 70 mg twice-daily dosing, with an improved safety profile.

The efficacy of dasatinib in patients with imatinib-resistant or -intolerant CML in myeloid blast crisis (MBC) or in lymphoid blast crisis (LBC) was evaluated in START-B and -L trials, respectively. In patients with MBC-CML, 32% experienced MaHR at 6-month follow-up, which increased to 34% at 8-month follow-up, and this rate was maintained at 12-month follow-up. MCyR was achieved in 31% of patients. In the LBC-CML group, 31% experienced MaHR at 6-month follow-up, which increased to 35% at 12-month follow-up. After a minimum follow-up of 12 months, MCyR was attained in 33% (MBP-CML) and 52% (LBP-CML) of patients and CCyR was attained in 26 and 46%, respectively. Median progression-free and overall survivals for patients with MBC were 6.7 and 11.8 months, respectively. In patients with LBC, the cor-
responding survival rates were 3.0 and 5.3 months, respectively. Recently, 2-year follow-up data from CA180-035 trial showed that dasatinib, 140 mg, once daily shows equivalent efficacy and improved safety compared with 70 mg, twice daily, in patients with CML in blast phase.\(^{31}\) Dasatinib induced cytogenetic and hematologic responses in a significant number of patients with imatinib-resistant CML (all phases), and was well tolerated in all of these studies. Dasatinib was associated with significant but reversible inhibition of platelet aggregation that may contribute to bleeding in some patients.\(^{32}\) Nonhematologic adverse events were mild to moderate, and cytopenias, although more common, were manageable with dose modification. Management of dasatinib toxicities are listed on pages 996 and 997.

Pleural effusion can be an adverse effect of dasatinib. Recently, Quintas-Cardama et al.\(^{33}\) from M. D. Anderson Cancer Center performed an analysis of patients with CML treated with varying doses of dasatinib in phase I and II studies. Pleural effusion occurred in 29% of patients with chronic-phase, 50% with accelerated-phase, and 33% with blast-phase CML; this led to dose interruption in 83% and dose reduction in 71%. Patients with prior cardiac history or hypertension and those receiving twice-daily dosing of dasatinib, 70 mg, are at increased risk for developing pleural effusion. Close monitoring and timely intervention is essential for continuing treatment with dasatinib.

Based on the favorable results of these 4 single-arm phase II studies, in June 2006 the FDA approved dasatinib (70 mg, twice daily) for use in patients with CML who are resistant or intolerant to imatinib.

In a recent dose-optimization randomized study, dasatinib dosed at 100 mg, once daily, was equally effective as 70 mg, twice daily, and was also associated with a lower incidence of any-grade pleural effusion (7% vs. 16%) and grade 3/4 thrombocytopenia (22% vs. 37%) in patients with chronic-phase CML who were resistant or intolerant to imatinib.\(^{34}\) Fewer patients required dose interruption (51% vs. 68%), dose reduction (30% vs. 55%), and toxicity-related discontinuation (16% vs. 23%). Data from 3-year follow-up confirmed the efficacy of dasatinib at 100 mg daily for patients with chronic-phase CML.\(^{35}\) At 36 months, progression-free and overall survival were 73% and 87%, respectively. CCyR rates were 39%, 45%, and 50% at 6, 12, and 24 months, respectively.

Based on the results of this study, the FDA approved dasatinib, 100 mg, once daily, as the starting dose for patients with chronic-phase CML. The recommended starting dose for patients with accelerated- or blast-phase CML was recently modified to 140 mg, once daily.

The efficacy and safety of dasatinib as first-line therapy in patients with previously untreated chronic-phase CML is being evaluated in an ongoing phase II trial.\(^{36}\) At a median follow-up of 24 months, 98% of evaluable patients had experienced CCyR. In historical comparison, the CCyR rates at 3, 6, and 12 months were comparable to those experienced with high-dose imatinib and better than those experienced with standard-dose imatinib. MMR occurred in 34% of patients at 12 months and 48% at 18 months. Dasatinib at a median daily dose of 100 mg as front-line therapy was also associated with a favorable safety profile. Large, ongoing randomized studies are comparing dasatinib, 100 mg, once daily with imatinib, 400 mg, once daily in patients with newly diagnosed chronic-phase CML.

Nilotinib

Nilotinib (formerly known as AMN107) is a new orally available, highly selective inhibitor of bcr-abl tyrosine kinase that is more potent than imatinib (20–50 times more potent in imatinib-resistant cell lines and 3–7 times more potent in imatinib-sensitive cell lines). In a phase I study, nilotinib was found to be active in imatinib-resistant CML with a favorable safety profile.\(^{37}\)

After this study, a phase II open-label trial evaluated the safety and efficacy of nilotinib in patients with imatinib-resistant or -intolerant chronic- and accelerated-phase CML. Nilotinib was administered at 400 mg, twice daily. The efficacy end point for chronic-phase CML was MCyR and the end point for accelerated-phase CML was MaHR. An interim analysis of 280 patients with chronic-phase CML at 6-month follow-up showed that 48% of patients experienced MCyR and 31% CCyR.\(^{38}\) Long-term follow-up results from this study recently confirmed that these responses are durable, with no change in safety profile.\(^{39}\) At a minimum follow-up of 19 months, CHR and MCyR were observed in 94% and 59% of patients, respectively. Median time to MCyR was 2.8 months. Responses were durable, with 78% patients maintaining MCyR at 24...
In October 2007, the FDA approved nilotinib (400 mg, twice daily) for the treatment of chronic- and accelerated-phase Ph-positive CML in adult patients resistant or intolerant to prior therapy with imatinib.

Nilotinib has also shown activity in a group of patients with blast-phase CML. In a phase II study of 136 patients, safety and efficacy data showed that CHR, MCyR, and CCyR were observed in 11%, 40%, and 29% of patients, respectively. Overall survival at 12 months was 42%. However, more than half of the patients discontinued treatment because of disease progression. Nilotinib is not yet approved by the FDA for the treatment of patients with blast-phase CML.

A multi-center phase II trial conducted by the GIMEMA CML Working Party evaluated the efficacy and safety of nilotinib as first-line therapy in early chronic-phase patients.\(^43\) In the intent-to-treat population, CHR rate at 3 and 6 months was 100% and 98%, respectively, at a median follow-up of 210 days. The CCyR rate at similar time points was 78% and 96%, respectively. After 1 month on treatment, 3% of patients experienced MMR, but this proportion increased rapidly over 6 months (22%, 59%, and 74% after 2, 3, and 6 months, respectively), with only 1 patient having the T315I mutation progressing to accelerated-blastic phase at 6 months.

**Conception**

Imatinib has been shown to be teratogenic and embryotoxic in animal studies. Some reports indicate that patients who receive imatinib at conception may have normal pregnancies.\(^44-50\)

In a study of 180 women exposed to imatinib during pregnancy, Pye et al.\(^44\) recently showed that 50% of pregnancies with known outcome were normal and 10% had fetal abnormalities; 18 pregnancies ended in spontaneous abortion. In another report, Ault et al.\(^45\) showed that among 10 women who discontinued imatinib because of pregnancy, 6 experienced an increase in Ph-positive metaphases. Only 3 women had CCyR at 18 months after resuming therapy.

Imatinib is not known to be genotoxic. However, spermatogenesis was impaired in animal studies. In the clinical experience, male fertility seems to be preserved in patients receiving imatinib.\(^51\) However, isolated reports of oligospermia have been seen in men undergoing imatinib therapy.\(^52,53\)
Dasatinib also has been shown to cause fetal toxicities in animals, but the effect of exposure during conception and pregnancy in humans is not known. Cortes et al. recently reported the outcome of pregnancies occurring among 16 patients (8 female, 8 male) who received dasatinib. Among the 8 female patients who became pregnant while on dasatinib, 3 had induced and 2 had spontaneous abortions. The outcome and pregnancy course in 3 patients were normal. Among the 8 male patients treated with dasatinib whose partners became pregnant while on treatment, normal pregnancy was reported in 7 cases and the outcome was unknown in 1.

Nilotinib caused embryonic and fetal toxicities in animals. No data describe the outcome of pregnancy in women taking nilotinib.

Currently, enough evidence is not available to favor the continuation of imatinib, dasatinib, or nilotinib during pregnancy. Potential benefit of tyrosine kinase inhibitor (TKI) therapy for the mother or its potential risk to the fetus must be carefully evaluated on an individual basis before imatinib, dasatinib, or nilotinib is administered to pregnant women. Men desiring conception should consider sperm cryopreservation before initiation of TKI therapy.

**Drug Interactions**

**Imatinib:** Imatinib is metabolized in the liver predominantly by the cytochrome P450 enzymes, CYP3A4 or CYP3A5. Drugs that induce CYP3A4/5 enzyme levels may decrease therapeutic levels of imatinib. CYP3A4/5-inducing drugs, such as anticonvulsants and steroids, should be used with caution in patients receiving imatinib, and appropriate alternatives should be explored to maximize treatment outcome. Conversely, drugs that inhibit CYP3A4 enzyme activity and those that are metabolized by the CY3A4/5 enzyme might result in increased plasma levels of imatinib. Imatinib is also a weak inhibitor of the CYP2D6 and CYP2C9 isoenzymes; therefore, drugs metabolized by these enzymes (e.g., warfarin) should be used with caution. See pages 993 through 995 for potential drug interactions with imatinib.

**Dasatinib:** Dasatinib is extensively metabolized in the liver, primarily by CYP3A4. CYP3A4 inducers may decrease plasma concentration of dasatinib. CYP3A4 inhibitors and drugs that are metabolized by this enzyme may increase the concentration of dasatinib. Therefore, concomitant administration with CYP3A4 inhibitors or inducers should be avoided. If co-administration cannot be avoided, a dose adjustment and close monitoring for toxicity should be considered. In addition, the solubility of dasatinib is pH-dependent, and long-term suppression of gastric acid secretion reduces dasatinib exposure. Concomitant use with H2 blockers or proton pump inhibitors is not recommended. See pages 996 and 997 for potential drug interactions with dasatinib.

**Nilotinib:** Nilotinib is also metabolized by the CYP3A4 isoenzyme, and drugs that induce CYP3A4 may decrease nilotinib plasma concentrations. If nilotinib must be administered with a CYP3A4 inducer, a dose increase should be considered. Concomitant administration of strong inhibitors of CYP3A4 may increase the concentration of nilotinib. If co-administration cannot be avoided, nilotinib should be interrupted or dose reduction should be considered. In addition, nilotinib is a competitive inhibitor of CYP2C8, CYP2C9, CYP2D6, and UGT1A1, potentially increasing the concentrations of drugs eliminated by these enzymes. See pages 998 and 999 for potential drug interactions with dasatinib.

**Chronic-Phase CML**

**Initial Workup**

The panel recommends the following tests as part of the initial evaluation of patients with chronic-phase CML (see page 986):

- History and physical
- CBC
- Platelet count
- Chemistry profile
- Bone marrow aspirate and biopsy

Bone marrow cytogenetics and measurement of BCR-ABL transcript levels using reverse transcriptase polymerase chain reaction (RT-PCR) are recommended before initiating treatment and for assessing response to therapy (see page 992). Conventional cytogenetics is recommended for initial workup because it detects karyotypic abnormalities other than the Ph chromosome.

Bone marrow is preferable for initial workup, not only to provide morphologic review but also to detect chromosomal abnormalities not detectable using peripheral blood. If collection of bone marrow is not feasible, fluorescent in situ hybridization (FISH) on a peripheral blood specimen with dual probes for...
BCR and ABL genes is an acceptable method for confirming the diagnosis of CML. Patients who are BCR-ABL−negative do not have CML, and have a significantly worse prognosis than those with BCR-ABL−positive disease. Therefore, further evaluation for other diseases is warranted for patients with BCR-ABL−negative disease. Patients whose cells are BCR-ABL−positive (according to karyotype analysis, FISH, or molecular techniques) are the focus of these NCCN guidelines.

**Primary Treatment**

These guidelines recommend primary treatment with imatinib mesylate for patients with newly diagnosed Ph-chromosome− or BCR-ABL−positive chronic-phase CML. The option of participating in a clinical trial should be discussed. NCCN member institutions believe that interferon should no longer be considered as initial therapy for CML, given the excellent long-term results with imatinib. Among patients treated with interferon, 10% to 15% experienced a CCyR with a median survival of more than 10 years; some of these patients may actually be cured. However, given this small percentage, most of the panel believed that this data for interferon did not outweigh the significant benefits seen with imatinib. Imatinib mesylate at a standard dose of 400 mg daily is a category 1 recommendation for initial treatment of CML (see page 986).

Interferon, pegylated interferon therapy, or participation in a clinical can be considered in rare patients who are not able to tolerate imatinib. Phase II/III studies showed that pegylated interferon−α interferon 2a and -2b were active as initial treatment in patients with chronic-phase CML.

**High-Dose Imatinib:** Most patients retain variable levels of residual molecular disease at the 400 mg dose of imatinib. Therefore, several studies have evaluated the impact of high-dose imatinib on patients with newly diagnosed CML. In a case series in which 114 patients with newly diagnosed CML were treated with 400 mg of imatinib, twice daily, MCyR was seen in 96% of patients and CCyR in 90%. Compared with standard-dose imatinib, high-dose imatinib was associated with significantly better CCyR rate ($P = .0005$), MMR rate (quantitative RT-PCR assay [qPCR] < 0.05%; $P = .00001$), and complete molecular response rate (undetectable bcr-abl; $P = .001$). High-dose imatinib was well tolerated but resulted 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 experienced progression to accelerated or blastic phase. Similar results were reported in a long-term follow-up study involving patients from 3 sequential trials.

The TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity) study is an open-label phase III randomized trial comparing the efficacy of a higher initial dose of imatinib and standard-dose imatinib in patients with newly diagnosed chronic-phase CML. This trial randomized 476 patients to receive either high-dose (800 mg) or standard-dose imatinib (400 mg).

Results of this study showed that significantly more patients receiving high-dose imatinib experienced MMR at 3 and 6 months, but not at 12 months, compared with those receiving standard-dose imatinib. Time to MMR and CCyR occurred faster in the high-dose arm than the standard-dose arm. At 12 months, MMR and CCyR rates in an intent-to-treat population were higher for the 800-mg dose but were no longer significantly statistically different (MMR, 46% vs. 40%, respectively; CCyR, 70% vs. 66%, respectively).

In patients with high Sokal risk scores, MMR rates at 12 months were 41% for those treated with high-dose imatinib compared with 26% for those treated with standard-dose imatinib. Earlier achievement of MMR correlated with imatinib plasma trough level at 1 month. Those with low imatinib concentrations (≤ 1165 ng/mL) experienced MMR more slowly than those with higher concentrations (≥ 1165 ng/mL). At 12 months, 85% of patients receiving 400 mg daily were receiving the randomized dose compared with 62% of those receiving 800 mg daily.

Hughes et al. also reported superior responses (MMR at 12 and 24 months were 55% and 77%, respectively) in patients receiving an initial dose of 600 mg of imatinib compared with those receiving less than 600 mg (MMR at 12 and 24 months were 32% and 53%, respectively).

The GIMEMA CML Working Party and the European LeukemiaNet study group have evaluated the efficacy of high-dose (800 mg) imatinib as front-line therapy in patients with chronic-phase CML having intermediate and high Sokal risk, respectively. The results of the phase II trial by the GIMEMA CML Working Party indicated that high-dose ima-
Primary Resistance: Primary hematologic resistance to imatinib therapy (failure to achieve hematologic remission within 3–6 months of initiation of treatment) is rare in patients with newly diagnosed Ph-positive chronic-phase CML, whereas primary cytogenetic resistance (failure to achieve any level of cytogenetic response at 6 months, MCyR at 12 months, or CCyR at 18 months) is evident in 15% to 25% of patients.

Available data indicate that inadequate plasma concentration of imatinib may be a cause of primary resistance. Gambacorti-Passerine et al. observed that excessive binding of imatinib to plasma protein AGP (alpha-1-glycoprotein) may reduce the therapeutic effect of imatinib. Picard et al. also observed that trough plasma levels of imatinib were significantly higher in patients experiencing CCyR and MMR at 12 months. In a subanalysis of the IRIS study, plasma levels of imatinib after the first month of treatment proved to be a significant prognostic factor for long-term clinical response. However, Ault et al. recently reported that plasma levels of imatinib in patients treated with different dose schedules had no correlation with response to therapy. The clinical value of monitoring plasma levels of imatinib has not been defined.

Overexpression of the multidrug resistance gene (MDR1) decreases the intracellular concentration of imatinib, which may confer resistance to imatinib. White et al. recently reported that most patients with suboptimal response to imatinib have low organic cation transporter-1 (OCT-1) activity. Their analysis of patients enrolled in the TIDEL and TOPS trial showed that those with high OCT-1 activity experienced excellent molecular response irrespective of the dose, and that response was highly dose-dependent in those with low OCT-1 activity. However, cellular uptake of dasatinib or nilotinib seems to be independent of OCT-1 expression. Secondary Resistance: The most common mechanism for secondary resistance is the reactivation of BCR-ABL activity, which occurs most often by mutations in the abl tyrosine kinase domain of the BCR-ABL gene (resulting in conformational changes in the fusion protein that affect the binding site of imatinib on the tyrosine kinase) and less frequently by BCR-ABL gene amplification, or increased BCR-ABL gene expression. Point mutations in the kinase domain are emerging as the most frequent mechanism.

Among mutations in the bcr-abl kinase domain, the presence of T315I mutation confers the highest resistance to imatinib, dasatinib, and nilotinib compared with resistance caused by other mutations. Some reports suggest that T315I is associated with disease progression and poor survival. In a recent study, Jabour et al. reported that survival of patients with T315I is dependent on the disease stage. At a median follow-up of 29 months after imatinib therapy, median survival has not been reached for chronic-phase CML (87% of patients were alive after 2 years). In the accelerated and blast phases, no differences in survival were seen between patients with T315I mutation and those with no mutations. Mutations in the ATP phosphate–binding loop (P-loop) have also been associated with poor prognosis among patients treated with imatinib. A large study of 319 patients in chronic phase found that any mutation, even with no other signs of resistance, was associated with both a loss of CCyR and a higher risk for progression compared with patients without a mutation (relative risk for loss of CCyR and progression, 3.8- and 3.7-fold, respectively). Patients with P-loop mutations were associated with a particularly high risk for progression. However, Jabour et al. could not confirm this finding. P-loop mutations were frequent in patients with accelerated- and blast-phase crisis. Although Branford et al. reported a higher incidence of mu-
mutations in patients with accelerated-phase CML, the difference in the frequency of mutation was significant between the early chronic and accelerated phases, compared with that between the accelerated and late chronic phases.\textsuperscript{75} In the START trials, dasatinib induced similar rates of major hematologic and cytogenetic responses irrespective of the presence of P-loop or other mutations in imatinib-resistant patients with accelerated- or blast-phase CML.\textsuperscript{26,39} Together, these data suggest that identification of mutations indicates a subgroup of patients that demand careful monitoring.

In the START-C study, 46\% of patients with imatinib-resistant chronic-phase CML did not carry BCR-ABL mutations, confirming that secondary resistance to imatinib is multifactorial. Other mechanisms that are independent of BCR-ABL include activation of the Src family of kinases (SFKs) or cytogenetic clonal evolutions characterized by additional chromosomal abnormalities in the Ph-positive cells.\textsuperscript{87,88}

Clonal evolutions are considered a feature of accelerated-phase CML. In a study from M. D. Anderson Cancer Center (before the use of imatinib), Majlis et al.\textsuperscript{89} analyzed patients who developed cytogenetic clonal evolution on interferon therapy. They concluded that the prognostic significance of clonal evolution is not uniform but is related to the specific chromosomal abnormality and the presence of other features of accelerated phase. In this study, presence of chromosome 17 abnormality, predominance of abnormal metaphases (\(\geq 36\%\)), and the other accelerated features were identified as the worst prognostic factors. Clonal evolution is associated with a better prognosis when it is considered the only criteria for disease progression compared with other accelerated features.\textsuperscript{90,91}

O’Dwyer et al.\textsuperscript{92} identified clonal evolution and failure to achieve MCyR by 6 months as adverse prognostic factors in patients with chronic-phase CML treated with imatinib.

Clonal cytogenetic abnormalities in Ph-negative cells have also been reported in a small subset of patients during imatinib therapy.\textsuperscript{93–96} The significance of these chromosomal abnormalities is unclear, but the most common includes trisomy 8, an aberration frequently seen in myelodysplastic syndrome. Only rare cases of myelodysplastic syndrome or acute myeloid leukemia (AML) have been reported in patients with CML, and these were usually in patients who were treated with interferon and prior chemotherapy. Some of these abnormalities may persist only in a small percentage of metaphases or may be transient and disappear with continued therapy in patients who have experienced CCyR. In a recent report, Deininger et al.\textsuperscript{97} concluded that the overall prognosis for patients with Ph-negative CML and clonal cytogenetic evolution in Ph-negative cells was good and dependent on the disease response to imatinib therapy. In patients with newly diagnosed chronic-phase CML treated with imatinib, 9\% of patients had chromosomal abnormalities in Ph-negative cells.\textsuperscript{98} Loss of Y chromosome was most common, although its significance in this setting is unclear. This phenomenon has been reported to be common in aging men.

Management of Resistance

Dose escalation of imatinib up to 800 mg daily has been shown to overcome some primary resistance, but the duration of responses typically has been short.\textsuperscript{99–101} Jabbour et al.\textsuperscript{102} assessed the long-term efficacy of imatinib dose escalation after hematologic or cytogenetic failure in 84 patients with chronic-phase CML. After a median follow-up of 61 months, the estimated 2- and 3-year EFS and overall survival rates were 57\% and 47\%, and 84\% and 76\%, respectively.

Responses were also durable; 88\% of patients with MCyR sustained their response beyond 2 years. Dose escalation was particularly effective in patients experiencing cytogenetic relapse for whom standard-dose imatinib induced a cytogenetic response. In this group of patients, CCyR and MCyR rates were 73\% and 87\%, respectively, compared with 52\% and 60\%, respectively, for the overall group of patients with cytogenetic failure. These results indicate that dose escalation of imatinib is unlikely to benefit patients experiencing hematologic failure or those who never experienced a cytogenetic response with standard-dose imatinib.

Kantarjian et al.\textsuperscript{103} recently performed a retrospective analysis of 106 patients with newly diagnosed chronic-phase CML from the IRIS trial treated with imatinib, 400 mg daily, who subsequently underwent dose escalation to either 600 or 800 mg daily. The rates of FFP to accelerated or blast phase and overall survival were 89\% and 84\%, respectively, at 3 years after dose increase.

Dasatinib and nilotinib have been effective
in patients with imatinib-resistant or -intolerant chronic-phase CML. The efficacy of high-dose imatinib and dasatinib were evaluated in a phase II trial (START-R) that randomized 150 patients with imatinib-resistant chronic-phase CML to receive 140 mg (70 mg twice a day) of dasatinib or 800 mg of imatinib. Median follow-up was 15 months. CHR was observed in 93% of patients receiving dasatinib compared with 82% randomized to high-dose imatinib. Dasatinib also showed higher MCyR rates (53% vs. 33%; \( P = .017 \)) and higher MMR rates (16% vs. 4%; \( P = .038 \)). Response rates were equivalent for high-dose imatinib and dasatinib in patients for whom treatment with 400 mg of imatinib failed, whereas dasatinib was clearly superior to 800 mg of imatinib if treatment with 600 mg of imatinib had already failed.

The 2-year follow-up data from this trial showed that duration of MCyR was greater with dasatinib. At 18 months, 90% of patients on dasatinib maintained MCyR compared with 75% on imatinib. At 24 months, time-to-treatment failure (proportion of patients without failure: 59% of patients on dasatinib vs. 18% on imatinib) and progression-free survival (86% for dasatinib vs. 65% for imatinib) were better for dasatinib, indicating that dasatinib is an effective treatment for patients with chronic-phase CML resistant to conventional imatinib doses.

Several new agents in clinical development have shown promising results in the management of patients with T315I mutation. Recently, some studies have reported the clinical activity of omacetaxine (OMA; homoharringtonine) in patients with CML after imatinib failure, including those with bcr-abl kinase domain mutations.

A multicenter open label phase II/III study is evaluating the safety and efficacy of OMA in imatinib-resistant CML in patients with T315I mutation. Preliminary results show that it is well tolerated and resulted in durable hematologic and cytogenetic responses in patients with chronic-phase CML. T315I transcripts were no longer detectable in 48% of the patients in chronic phase; CHR was seen in 85% of patients, and 28% experienced cytogenetic responses (15% CCyR and 10% MCyR). Estimated 2-year progression-free survival is 70%. Median duration of CHR, MCyR, and CCyR is 8.9, 6.1, and 7.4 months, respectively.

### Monitoring Response in CML

Disease monitoring to assess the response to therapy and to detect early relapse is one of the key management strategies of CML. Response to therapy can be of 3 different types (see page 996): hematologic, cytogenetic, and molecular. A widely accepted goal of CML therapy is for patients to experience CCyR within 18 months of initiation of therapy.

#### Hematologic Response

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

#### Cytogenetic Response

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

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

Hypermetaphase FISH is more sensitive and can analyze up to 500 metaphases at a time. Techniques such as double-FISH can detect all variant translocations of the Ph chromosome and are also associated with low false-positive rates. FISH can be used complimentary to conventional cytogenetics until FISH levels are less than 5% to 10%. This technique is no longer useful for monitoring further reduction in Ph levels. At this point, more sensitive techniques are required.

Cytogenetic responses indicate treatment effectiveness. In the IRIS study, progression-free survival was significantly better for patients who experienced any cytogenetic response at 6 months and an MCyR at 12 months compared with those with no cytogenetic response at 6 months, or less than an MCyR at 12 months. At the median follow-up of 60 months, progression-free survival rate was better for patients who experienced a CCyR or partial cytogenetic response at 12 months (97% and 93%, respectively) than for those who did not have a MCyR at 12 months (81%). At 7 years, of the 456 patients who experienced CCyR on imatinib, only 15 patients (3%) progressed to accelerated or blast phase during study treatment.

de Lavallade et al. also identified cytogenetic response after 1 year of imatinib therapy as the major prognostic factor for overall and progression-free survival. In a retrospective analysis of data from phase II studies of dasatinib in patients with imatinib-resistant chronic-phase CML, EFS was higher for those who started dasatinib after losing MCyR on imatinib than for those who received dasatinib after the loss of both MCyR and CHR (89% and 29%, respectively).

These guidelines recommend cytogenetic evaluation at 6, 12, and 18 months after imatinib therapy. If a CCyR is experienced at either of the earlier time points, then conventional cytogenetics need not be repeated. If a persistent, unexplained, drop in blood counts occurs during therapy, it may be reasonable to perform a bone marrow and cytogenetic evaluation to look for non-Ph clonal changes and evidence of myelodysplasia.

Molecular Response
Molecular response is determined by the decrease in the amount of BCR-ABL chimeric mRNA. Complete molecular response occurs when no BCR-ABL chimeric mRNA is detected with RT-PCR. MMR indicates a reduction (≥ 3-log reduction) of BCR-ABL chimeric mRNA.

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 the bone marrow, and can detect one CML cell in a background of 100,000 or more normal cells. Most patients initially treated with imatinib or allogeneic transplant will experience a CCyR; however, a smaller percentage will experience a complete molecular response identified by the absence of BCR-ABL mRNA transcripts. The BCR-ABL mRNA transcripts typically fall slowly after complete cytogenetic remission is reached. Therefore, RT-PCR assays are useful for establishing a baseline BCR-ABL for monitoring molecular responses after patients experience CCyR.

Qualitative RT-PCR technique is reported as either positive or negative. In contrast, a qPCR assay reports the actual percentage of BCR-ABL mRNA transcripts. Another advantage of the qPCR assay is the strong correlation between results obtained from the peripheral blood and the bone marrow, allowing minimal residual disease monitoring without the need for obtaining bone marrow aspirations.

Several studies have reported the prognostic significance of molecular response. MMR is associated with durable long-term remission rates and progression-free survival after treatment with imatinib. The 5-year follow-up of the IRIS trial showed that no patient who had a CCyR and MMR at 12 months experienced progression to the accelerated or blast phase. The estimated progression-free survival rate at 24 months was 100% for patients with a CCyR and at least a 3-log reduction in the BCR-ABL transcript level at 12 months, compared with 95% for those with CCyR and a less than 3-log reduction of BCR-ABL at 12 months.

The 6-year follow-up of the IRIS study also showed that progression is rare in patients who experienced MMR at any time point during imatinib therapy. The estimated EFS rate at 72 months was 98% for patients who had an MMR at 18 months compared with 89% in those with no MMR. Press et al. also showed that failure to achieve at least a 2-log reduction in BCR-ABL mRNA at CCyR or a 3-log
Monitoring Response to Imatinib Therapy

Most patients receiving imatinib as initial treatment for CML will experience a complete hematologic response at 3 months and a CCyR at 6, 12, or 18 months. If no hematologic and cytogenetic response occurs at these intervals, mutational analysis should be considered and patient compliance to imatinib therapy evaluated. Treatment interruptions and nonadherence to imatinib might lead to undesirable clinical outcomes. Patient education on adherence to imatinib therapy and close monitoring of this adherence is critical to achieve optimal responses.128,129 The optimal guidelines for monitoring response to imatinib therapy are detailed on page 992.

Cytogenetic evaluation is recommended at 6 and 12 months from initiation of treatment, when the patient seems to be responding to treatment. If a CCyR is reached at 6 months, cytogenetic evaluation does not need to be repeated at 12 months. If the patient is not experiencing a complete cytogenetic remission at 12 months but has had a partial cytogenetic remission (1%–35% Ph metaphases), repeat cytogenetic testing is recommended at 18 months.

A rising BCR-ABL level may be associated with an increased risk for the emergence of BCR-ABL mutation in the future. Kantarjian et al.110 recently analyzed the significance of rising BCR-ABL transcript levels determined with qPCR. In this analysis, most patients showing significant qPCR increases remained in CCyR. Only 13 of 116 patients with significant qPCR increases experienced CML progression, including 11 who either lost or never had an MMR and showed more than a 1-log increase of qPCR. Thus, this group of patients should be monitored more closely, and may be evaluated for mutations of bcr-abl kinase domain and considered for investigational therapeutic interventions.

The guidelines recommend that BCR-ABL transcript levels should be measured every 3 months when the patient seems to be experiencing response to imatinib, and every 3 to 6 months when a CCyR is reached.111 If a patient has a rising level of BCR-ABL transcripts (1-log increase) with an MMR, qPCR analysis should be repeated in 1 to 3 months. If no MMR is seen, then bone marrow cytogenetics is recommended.

Identification of mutations supports the diagnosis of imatinib resistance. Mutational analysis would be helpful in identifying the subset of patients who will be eligible for treatment with dasatinib or nilotinib, allogeneic stem cell transplant, or clinical trial. abl Kinase domain mutational analysis may provide additional information if there is an inadequate response (failure to experience CHR at 3 months, minimal cytogenetic response at 6 months, or MCyR at 12 months) or any signs of loss of response (defined as hematologic or cytogenetic relapse).

Follow-up Therapy for Patients Receiving Imatinib

In rare patients unable to tolerate high-dose imatinib, dasatinib, or nilotinib, interferon or PEG-interferon...
therapy or participation in a clinical trial can be considered. Participation in a clinical trial is a reasonable treatment option for patients with T315I mutation.

3-Month Follow-up (page 987)
- Patients who experience hematologic remission continue on the same dose of imatinib and are re-evaluated at 6 months with bone marrow cytogenetics.
- Dasatinib or nilotinib is recommended as one of the treatment options for patients experiencing no hematologic remission or if they have hematologic relapse. Patients should consider participation in clinical trials.

6-Month Follow-up (page 987)
- Patients experiencing CCyR or partial or minor cytogenetic response continue on the same dose of imatinib.
- Dose escalation of imatinib to a maximum dose of 800 mg, as tolerated, is an alternate option for those experiencing a minor cytogenetic response.
- Patients experiencing no cytogenetic response can be switched to dasatinib or nilotinib. Patients should consider participation in clinical trials.

12-Month Follow-up (page 988)
- If a CCyR or partial cytogenetic response is detected, the same dose of imatinib is continued.
- Dose escalation of imatinib to a maximum of 800 mg, as tolerated, is an alternate option for those experiencing partial cytogenetic response.
- Dasatinib or nilotinib is recommended for patients experiencing minor or no cytogenetic response. Patients should consider participation in clinical trials.
- Dose escalation to a maximum dasatinib or nilotinib dose of 800 mg, as tolerated, or participation in a clinical trial can be considered for those experiencing cytogenetic relapse.

18-Month Follow-up (page 989)
- Continuation of imatinib at the initial dose is recommended for those experiencing CCyR.
- Treatment options for those experiencing partial cytogenetic response or a cytogenetic relapse include dose escalation of imatinib to a maximum of 800 mg; dasatinib or nilotinib; or participation in a clinical trial.
- Dasatinib or nilotinib, or participation in a clinical trial can be considered for those experiencing a minor or no cytogenetic response.

Discontinuation of Imatinib
Imatinib has become standard front-line treatment for patients with CML; most patients in chronic-phase can experience a CCyR. Results of the IRIS study suggest that the annual mortality rate among patients with CML receiving imatinib is less than 5% in the first 5 to 6 years of treatment, compared with 10% to 20% in the pre-imatinib era. However, the disease usually relapses if imatinib therapy is stopped even in patients who experience complete response.

Rousselot et al. suggested that discontinuation of imatinib is feasible in a subset of patients experiencing sustained complete molecular response. A recent report from the Multicentre Stop Imatinib (STIM) study confirmed that treatment can be stopped in patients experiencing sustained complete molecular response (CMR) and can be maintained after discontinuation of imatinib, especially in patients who received prior interferon with long-term follow-up.

Ross et al. also concluded that imatinib withdrawal in patients with stable CMR is safe when performed with close molecular monitoring. However, the sample size was small (N = 18) and follow-up was short. Thus, investigators recommend that imatinib should be withdrawn only in the setting of a clinical trial.

Additional prospective studies are needed to determine the optimal duration of imatinib therapy. Currently, discontinuation of therapy is not recommended outside the context of a clinical trial for patients whose CML is responding to imatinib.

Monitoring Response to Dasatinib or Nilotinib Therapy
Early cytogenetic response to second-generation TKIs can predict survival and guide subsequent therapy. Tam et al. analyzed the significance of cytogenetic response in patients treated with dasatinib or nilotinib. After 12 months of treatment, patients experiencing MCyR had a significant advantage over those experiencing minor cytogenetic response or CHR. Thus, patients receiving dasatinib or nilotinib with no cytogenetic response at 3 or 6 months should be considered for alternative therapies.

Branford et al. and Milojkovic et al. recently reported that the measurement of BCR-ABL transcript level at 3 months after the switch could predict response to second-generation TKIs and provide further information about the value of continuing treatment with these agents.
Disease Progression While on Imatinib

Disease progression is defined as loss of hematologic or cytogenetic response or progression to accelerated or blast phase (lymphoid or myeloid).

The panel did not reach uniform consensus about the definition of accelerated-phase CML; therefore, 4 different definitions are provided in the guidelines (page 986). Clinical trials of TKIs have largely reported efficacy data using the M. D. Anderson Cancer Center disease-phase criteria. Dasatinib or nilotinib, followed by allogeneic hematopoietic stem cell transplant (HSCT), if feasible, is recommended for disease progression to accelerated-phase after imatinib therapy (page 991).

CML in lymphoid blast phase is pathologically similar to Ph-positive ALL. According to the International Bone Marrow Transplant Registry (IBMTR), blast crisis is defined as 30% or greater blasts in the blood, bone marrow, or both, or as the presence of extramedullary disease. WHO criteria for blast crisis were also incorporated into the algorithm (page 1001).

Dasatinib either alone or in combination with chemotherapy, followed by allogeneic HSCT, if feasible, is recommended for patients in myeloid or lymphoid blast phase (page 991). An ALL-type induction therapy is appropriate for those with an LBC, whereas an AML-type induction therapy is appropriate for those with an MBC. See the NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia for treatment options (to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org). Participation in a clinical trial is another option for patients experiencing disease progression.

The addition of imatinib or dasatinib to chemotherapy has been shown to improve outcome in patients with de novo or minimally treated or newly diagnosed Ph-positive ALL. In patients presenting with de novo Ph-positive ALL, imatinib or dasatinib can be given in combination with chemotherapy or as monotherapy for those who are not candidates for chemotherapy.

Allogeneic HSCT

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

Ongoing advances in alternative donor sources (e.g., unrelated donors and cord blood), more accurate human leukocyte antigen 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 human leukocyte antigen typing has enabled a rigorous and stringent selection of unrelated matched donors, and this improvement in typing has translated into greatly improved transplant outcomes, so that results with unrelated, fully matched donors are comparable to those of matched donors.

The potential use of transplantation must be tied to faithful monitoring of disease, because the major potential pitfall in delaying transplantation is missing the chronic-phase interval. Outcome is clearly better for patients in chronic phase who undergo transplantation compared with those 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.

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

Concern has been shown that previous treatment with imatinib might have a deleterious effect on subsequent transplant outcomes, as previously implicated with busulfan and interferon. However, several large studies that have examined the use of imatinib before transplantation have found no significant increase in death, relapse rate, and nonrelapse mortality compared with cases who did not receive pretransplant imatinib. These data suggest that pretransplant imatinib does not compromise the outcome of a subsequent allogeneic transplant. In fact, IBMTR data showed that prior use of imatinib was associated with improved survival in patients with chronic-phase CML who underwent transplan-
tion. Some studies have also shown that using a second-generation TKI before allogeneic HSCT does not affect the outcome of transplantation nor does it increase transplant-related toxicity.

NCCN Recommendations for Allogeneic HSCT

Chronic-Phase CML: NCCN recommendations have changed since the 5-year follow-up data of the IRIS trial showed excellent survival benefit for imatinib. Allogeneic HSCT is no longer recommended as a first-line treatment for chronic-phase CML. The role of HSCT in the treatment of CML should be discussed with patients (page 986). Allogeneic HSCT is recommended for patients with T315I mutation whose disease does not respond to imatinib, dasatinib, or nilotinib. Nonmyeloablative transplantation is investigational and should be performed only in the context of a clinical trial.

Evaluation for allogeneic HSCT is recommended for all patients who have experienced inadequate response (as listed below) to standard-dose imatinib:

- No hematologic remission or experiencing hematologic relapse at 3 months (page 987).
- No cytogenetic response at 6 months (page 987).
- Minor or no cytogenetic response or experiencing cytogenetic relapse at 12 months (page 988).
- Partial, minor, or no cytogenetic response, or experiencing cytogenetic relapse at 18 months (page 989).

Disease Progression: Allogeneic HSCT is a consideration for patients experiencing disease progression on imatinib and for those presenting with CML in accelerated phase or blast crisis (page 991). In patients with disease progression on imatinib therapy, treatment with a course of dasatinib or nilotinib is beneficial as a “bridge” to transplantation.

Follow-up Therapy: Donor lymphocyte infusion (DLI) is effective in inducing remissions in patients with relapsed CML after allogeneic HSCT, although it is more effective in chronic than advanced phase. DLI induces complete remissions in most patients with CML in early-stage relapse. DLI is also associated with complications such as graft-versus-host disease (GVHD), susceptibility to infections, and immunosuppression. Improved methods for detecting BCR-ABL transcripts to predict relapse, modified delivery of lymphocytes through deleting CD8+ cells and escalating doses of donor T cells, and the development of reduced-intensity conditioning regimens have reduced the incidence of GVHD.

Recently, imatinib was shown to be effective in inducing remissions, particularly in patients with relapsed chronic-phase CML after allogeneic HSCT. However, in a recent retrospective analysis, disease-free survival was significantly higher in patients receiving DLI than those treated with imatinib. A trend was also seen toward higher rates of complete molecular remissions in the DLI group. These observations have not been confirmed in randomized trials. In patients for whom previous treatment with imatinib failed, no data support the use of posttransplant imatinib. Other TKIs, such as dasatinib or nilotinib, may be more appropriate. For patients who undergo allogeneic HSCT for blast-phase CML in first remission, imatinib or dasatinib can be used as maintenance therapy posttransplant. Dasatinib has been shown to eradicate central nervous system leukemia.

NCCN Recommendations

Monitored withdrawal of immune suppression is recommended for patients who are not experiencing remission or are undergoing cytogenetic relapse after allogeneic HSCT. Patients experiencing cytogenetic remission after allogeneic HSCT are followed up with qPCR monitoring to determine the presence or absence of BCR-ABL. Using qPCR after transplant for early detection of BCR-ABL transcripts is useful to predict outcome and define further treatment options. A qualitative RT-PCR assay positive for BCR-ABL is associated with a high risk for relapse, especially 6 to 12 months after transplantation and in the setting of T-cell depletion. The guidelines recommend PCR monitoring every 3 months for 2 years, then every 6 months for 3 years (page 990).

Discussion of transplant options with a transplant team is recommended for patients who are experiencing cytogenetic relapse. Imatinib, dasatinib, DLI, or interferon can be considered alternate treatment options (page 990). Participation in a clinical trial should be considered.

Summary

CML is a hematopoietic stem cell disease characterized by the presence of 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 imatinib’s safety, efficacy, and excellent survival benefit in patients with newly diagnosed CML. At an initial standard dose of 400 mg daily, imatinib mesylate is the standard first-line treatment for newly diagnosed chronic-phase CML. Higher doses, if tolerated, can be administered for patients experiencing relapse. Monitoring treatment response with cytogenetics and RT-PCR is crucial in CML to assess response to treatment and detect resistance. The NCCN guidelines recommend monitoring response to imatinib therapy at 3, 6, 12, and 18 months.

Primary hematologic resistance to imatinib is rare in patients with newly diagnosed CML, whereas primary cytogenetic resistance is observed in 15% to 25% of patients. Additionally, some patients will eventually develop secondary resistance related to the presence of mutation in the BCR-ABL gene, resulting in disease progression on imatinib. Dose escalation of imatinib has been shown to overcome resistance in some patients with cytogenetic failure on standard-dose imatinib, particularly those with prior cytogenetic response. Second-line TKIs, 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 patients whose disease progresses to accelerated phase while on imatinib therapy, or for those with chronic-phase CML that is refractory to imatinib, whereas only dasatinib is recommended for those whose disease progresses to blast phase while on imatinib therapy.

Allogeneic HSCT is indicated only for patients with inadequate or no response to imatinib therapy, and those whose disease progresses on imatinib. For most patients, a trial of dasatinib or nilotinib is reasonable before proceeding to allogeneic HSCT.

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

References
Lipton JH, Khoroshko N, Golenkov A, et al. Phase II, randomized,
Guo JQ, Wang JYG, Arlinghaus RB. Detection of BCR-ABL
Seymour JF, Grigg A, Reynolds J, et al. Two year data from a
Seshadri T, Seymour JF, McArthur GA. Oligospermia in a patient

its pharmacokinetics in chronic myeloid leukemia patients. Clin
glycoprotein binds to imatinib (STI571) and substantially alters
its pharmacokinetics in chronic myeloid leukemia patients. Clin


Philadelphia-positive chronic myeloid leukemia: a European
400 mg and 800 mg daily in the front-line treatment of high-risk,
leukemia patients in early chronic phase: a phase 2 trial of the

affected chronic myeloid leukemia patients (pts) with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase (CML-CP) using molecular endpoints: 1-year results of TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity) study [abstract]. Blood 2008;112:Abstract 335.

70. White DL, Saunders VA, Dang P, et al. Most CML patients who have a suboptimal response to imatinib have low OCT-1 activity: higher doses of imatinib may overcome the negative impact of low OCT-1 activity. Blood 2007;110:4064–4072.
Chronic Myelogenous Leukemia


100. Marin D, Goldman JM, Olavarria E, Apperley JF. Transient benefit only from increasing the imatinib dose in CML patients who do not achieve complete cytogenetic remissions on conventional doses. Blood 2003;102:2702–2704.


Chronic Myelogenous Leukemia


131. Branford S, Ruddick Z, Parkinson I, et al. Real time quantitative PCR analysis can be used as a primary screen to identify patients with CML treated with imatinib who have BCR-ABL kinase domain mutations. Blood 2004;104:2926–2932.


140. Milojkovic D, Bua M, Apperley JE, et al. Prediction of cytogenetic response to second generation TKI therapy in CML chronic...
phase patients who have failed imatinib therapy and early identification of factors that influence survival [abstract]. Blood 2008;112:Abstract 332.


Chronic Myelogenous Leukemia


### Individual Disclosures of the NCCN Chronic Myelogenous Leukemia Panel

<table>
<thead>
<tr>
<th>Panel Member</th>
<th>Clinical Research Support</th>
<th>Advisory Boards, Speakers Bureau, Expert Witness, or Consultant</th>
<th>Patent, Equity, or Royalty</th>
<th>Other</th>
<th>Date Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellin Berman, MD</td>
<td>Novartis Pharmaceuticals Corporation</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>12/15/08</td>
</tr>
<tr>
<td>Hossein Borghaei, DO, MS</td>
<td>Genentech, Inc.; and Spectrum Amgen Inc.; Eli Lilly and Company; and Genentech, Inc.</td>
<td>Bristol-Myers Squibb Company; and Celgene Corporation; Novartis Pharmaceuticals Corporation; and Pharmion Corporation</td>
<td>None</td>
<td>None</td>
<td>10/2/09</td>
</tr>
<tr>
<td>Daniel J. DeAngelo, MD, PhD</td>
<td>None</td>
<td>Bristol-Myers Squibb Company; and Celgene Corporation; Novartis Pharmaceuticals Corporation; and Pharmion Corporation</td>
<td>None</td>
<td>None</td>
<td>12/15/08</td>
</tr>
<tr>
<td>Marcel P. DeVetten, MD</td>
<td>None</td>
<td>Bristol-Myers Squibb Company; and Novartis Pharmaceuticals Corporation</td>
<td>None</td>
<td>None</td>
<td>3/28/08</td>
</tr>
<tr>
<td>Steven Devine, MD</td>
<td>Genzyme Corporation</td>
<td>None</td>
<td>National Cancer Institute</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harry P. Erba, MD, PhD</td>
<td>Cephalon, Inc.; Eli Lilly and Company; Exelixis Inc.; Genzyme Corporation; Kanisa Pharmaceuticals Corporation; Wyeth Pharmaceuticals; and Xantheus Pharmaceuticals, Inc.</td>
<td>Bristol-Myers Squibb Company; Celgene Corporation; Novartis Pharmaceuticals Corporation; and Pharmion Corporation</td>
<td>None</td>
<td>None</td>
<td>7/28/09</td>
</tr>
<tr>
<td>Jason Gotlib, MD, MS</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>9/30/09</td>
</tr>
<tr>
<td>Madan Jagasia, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>10/1/09</td>
</tr>
<tr>
<td>Joseph O. Moore, MD</td>
<td>Genentech, Inc.; and Novartis Pharmaceuticals Corporation</td>
<td>Bristol-Myers Squibb Company; and Novartis Pharmaceuticals Corporation</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Tariq I. Mughal, MD, FRCP</td>
<td>Celgene Corporation; and Novartis Pharmaceuticals Corporation</td>
<td>Bristol-Myers Squibb Company; Celgene Corporation; and Novartis Pharmaceuticals Corporation</td>
<td>None</td>
<td>None</td>
<td>10/7/09</td>
</tr>
<tr>
<td>Susan O'Brien, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/1/09</td>
</tr>
<tr>
<td>Javier Pinilla-Ibarz, MD, PhD</td>
<td>Bristol-Myers Squibb Company; Exelixis Inc.; Novartis Pharmaceuticals Corporation; and Innovative</td>
<td>Bristol-Myers Squibb Company; and Novartis Pharmaceuticals Corporation</td>
<td>None</td>
<td>None</td>
<td>9/10/08</td>
</tr>
<tr>
<td>Jerald P. Radich, MD</td>
<td>Bristol-Myers Squibb Company; and Novartis Pharmaceuticals Corporation</td>
<td>Bristol-Myers Squibb Company; and Novartis Pharmaceuticals Corporation</td>
<td>None</td>
<td>None</td>
<td>11/13/08</td>
</tr>
<tr>
<td>Neil P. Shah, MD, PhD</td>
<td>Pending</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Paul J. Shami, MD</td>
<td>Genzyme Corporation</td>
<td>Novartis Pharmaceuticals Corporation</td>
<td>JK Therapeutics Inc.</td>
<td></td>
<td>4/1/08</td>
</tr>
<tr>
<td>B. Douglas Smith, MD</td>
<td>Bayer Healthcare; Cephalon, Inc.; Novartis Pharmaceuticals Corporation</td>
<td>Bristol-Myers Squibb Company; and Novartis Pharmaceuticals Corporation</td>
<td>None</td>
<td>None</td>
<td>7/31/09</td>
</tr>
<tr>
<td>David S. Snyder, MD</td>
<td>Bristol-Myers Squibb Company; and Novartis Pharmaceuticals Corporation</td>
<td>Bristol-Myers Squibb Company; and Novartis Pharmaceuticals Corporation</td>
<td>None</td>
<td>None</td>
<td>7/1/09</td>
</tr>
<tr>
<td>Martin S. Tallman, MD</td>
<td>None</td>
<td>Genzyme Corporation</td>
<td>None</td>
<td>None</td>
<td>9/28/09</td>
</tr>
<tr>
<td>Moshe Talpaz, MD</td>
<td>None</td>
<td>Ariad Pharmaceuticals, Inc.; and Novartis Pharmaceuticals Corporation</td>
<td>None</td>
<td>None</td>
<td>1/5/09</td>
</tr>
<tr>
<td>Meir Wetzler, MD</td>
<td>Cephalon, Inc.; and Genzyme Corporation</td>
<td>Bristol-Myers Squibb Company; and Novartis Pharmaceuticals Corporation</td>
<td>None</td>
<td>None</td>
<td>9/5/08</td>
</tr>
</tbody>
</table>

The NCCN guidelines staff have no conflicts to disclose.

*Information not available at printing. Please go to www.nccn.org for updates.