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Chronic Myelogenous Leukemia, Version 1.2015

Clinical Practice Guidelines in Oncology

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Abstract

Chronic myelogenous leukemia (CML) is usually diagnosed in the chronic phase. Untreated chronic phase CML will eventually progress to advanced phase (accelerated or blast phase) CML. Tyrosine kinase inhibitors (TKIs) have been shown to induce favorable response rates in patients with accelerated and blast phase CML. The addition of TKIs to chemotherapy has also been associated with improved outcomes in patients with blast phase CML. Allogeneic hematopoietic stem cell transplant remains a potentially curative option for patients with advanced phase CML, although treatment with a course of TKIs will be beneficial as a bridge to transplant. This manuscript discusses the recommendations outlined in the NCCN Guidelines for the diagnosis and management of patients with advanced phase CML. (*J Natl Compr Canc Netw* 2014;12:1590–1610)

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

Overview

Chronic myelogenous leukemia (CML) accounts for 15% of adult leukemias. The median age at disease onset is 67 years; however, SEER statistics show that CML occurs in all age groups.[1] In 2014, an estimated 5980 people will be diagnosed with CML in the United States, and 810 people will die from the disease.[2]

CML is characterized by the presence of Philadelphia chromosome (Ph) resulting from a reciprocal translocation between chromosomes 9 and 22 [t(9;22)]. 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 (*ABL1*) gene located on chromosome 9 at band

Please Note

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Individual disclosures for the NCCN Chronic Myelogenous Leukemia Panel members can be found on page 1610. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

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q34.[3] The product of the *BCR-ABL1* fusion gene, p210, which is a fusion protein with deregulated tyrosine kinase activity, plays a central role in the pathogenesis of CML. Another fusion protein, p190, is also produced, usually in the setting of Ph+ acute lymphoblastic leukemia (ALL). p190 is detected in only 1% of all patients with CML.[4]

CML occurs in 3 different phases (chronic, accelerated, and blast phase) and is usually diagnosed in the chronic phase. Untreated chronic phase CML (CP-CML) will eventually progress to advanced phase in 3 to 5 years.[5] Gene expression profiling has shown a close correlation of gene expression between accelerated phase CML (AP-CML) and blast phase CML (BP-CML). The bulk of the genetic changes in progression occur in the transition from CP-CML to AP-CML.[6] The activation of the β-catenin signaling pathway in CML granulocyte-macrophage progenitors (which enhances the self-renewal activity and leukemic potential of these cells) may also be a key pathobiologic event in the evolution to BP-CML.[7]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CML discuss the clinical management of CML in all 3 phases (chronic, accelerated, and blast phase). This manuscript discusses the management of advanced phase CML.

Advanced Phase CML

Accelerated Phase

Varying definitions have been used for AP-CML (see CML-K, page 1597).[8–13] The most commonly used

Text cont. on page 1598.

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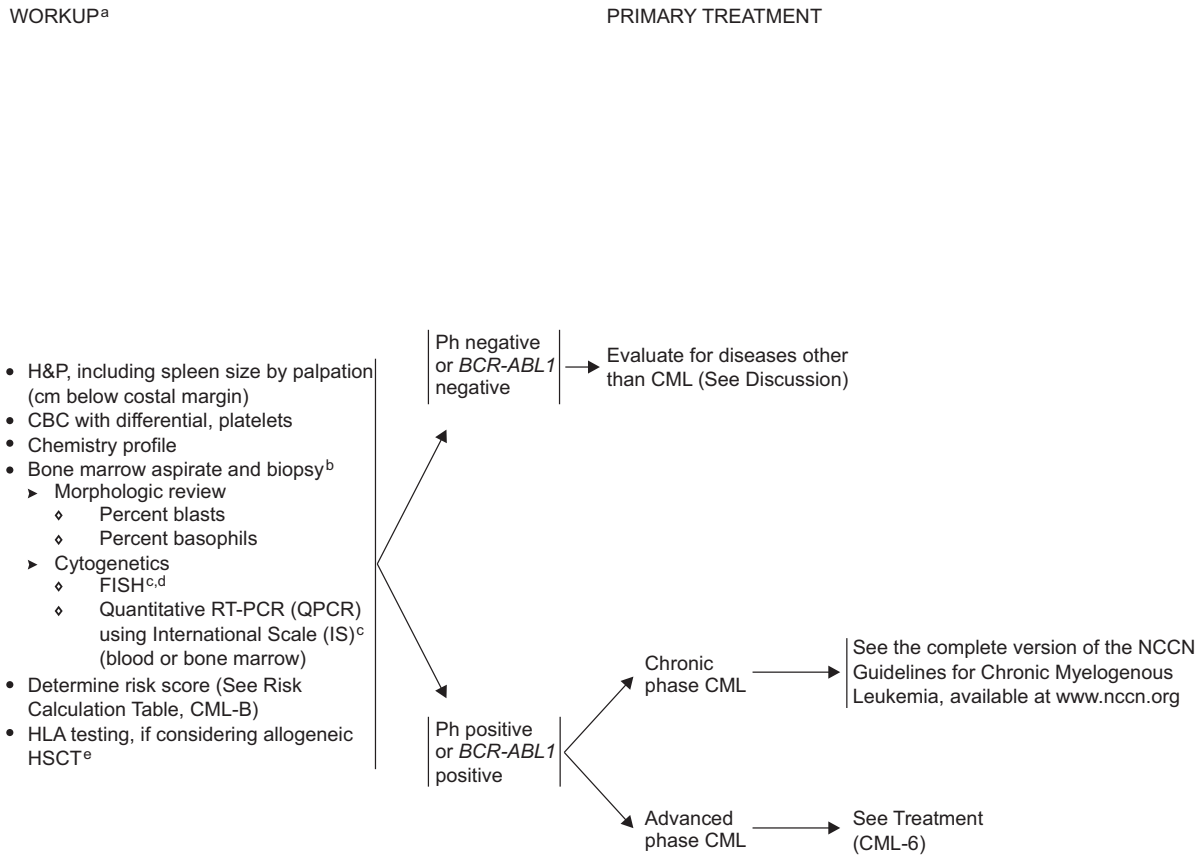

[a] See Recommendations for Monitoring Response to TKI Therapy and Mutational Analysis (CML-A; available online, in these guidelines, at NCCN.org).
[b] Bone marrow should be done for the initial workup, not only to provide morphologic review, but also to detect chromosomal abnormalities that are not detectable on peripheral blood FISH.
[c] See Discussion for further details.
[d] FISH on peripheral blood, if collection of bone marrow is not feasible.
[e] Indications and outcomes of allogeneic HSCT are dependent on age, donor type, and transplant center. Nonmyeloablative HSCT is under investigation and should be performed only in the context of a clinical trial.

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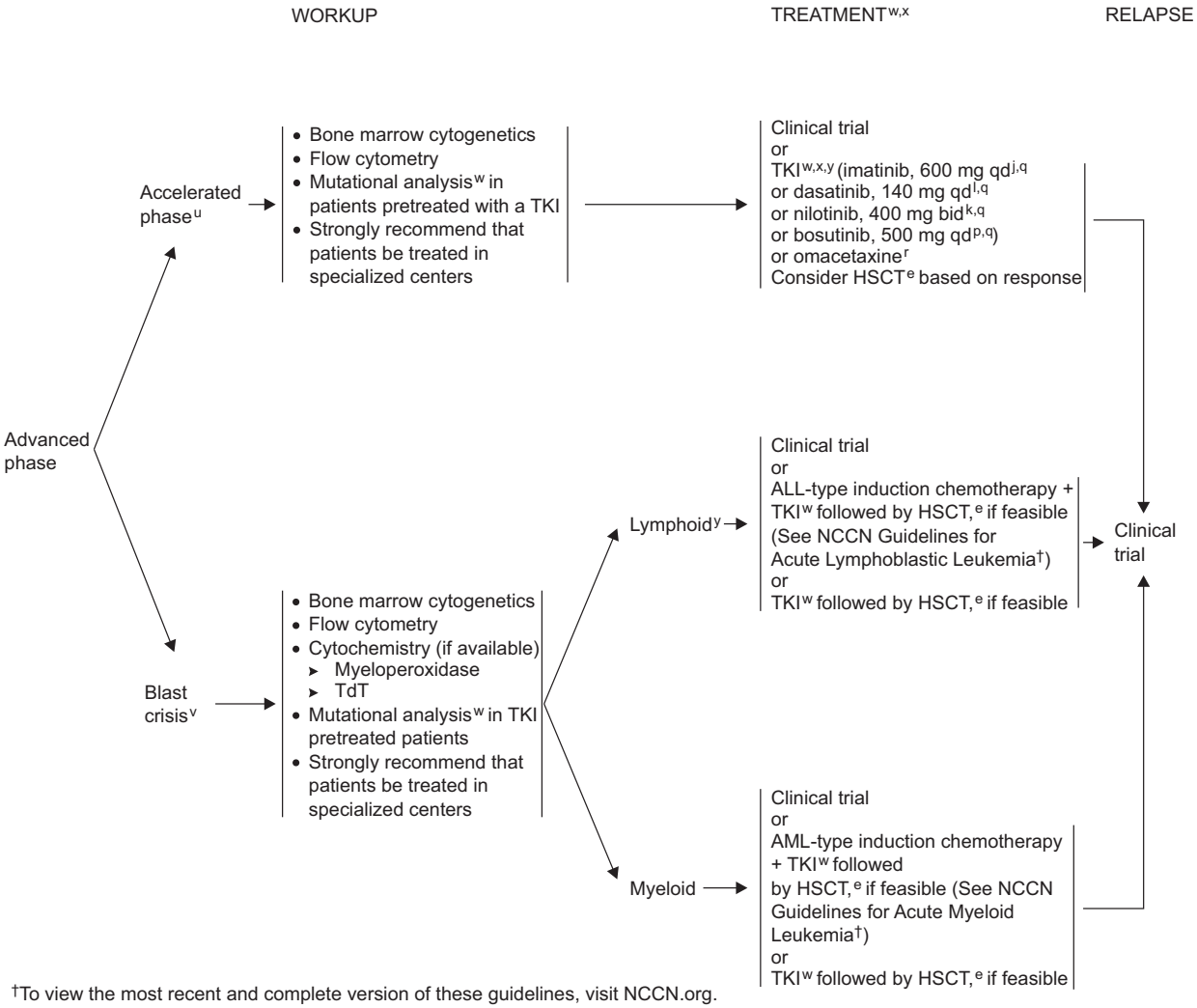

[†]To view the most recent and complete version of these guidelines, visit NCCN.org.

[e]Indications and outcomes of allogeneic HSCT are dependent on age, donor type, and transplant center. Nonmyeloablative HSCT is under investigation and should be performed only in the context of a clinical trial.
[j]See Management of Imatinib Toxicity (CML-D*).
[k]See Management of Nilotinib Toxicity (CML-E*).
[l]See Management of Dasatinib Toxicity (CML-F*).
[p]See Management of Bosutinib Toxicity (CML-G*).
[q]Patients treated with first-line imatinib should be treated with nilotinib, dasatinib, or bosutinib in the second-line setting. Patients treated with first-line nilotinib or dasatinib could be treated with an alternate TKI (other than imatinib) in the second-line setting.
[r]Omacetaxine is a treatment option for patients with resistance and/or intolerance to ≥2 TKIs. See Management of Omacetaxine Toxicity (CML-H*).
[u]See Definitions of Accelerated Phase (CML-K).
[v]See Definitions of Blast Crisis (CML-L*).
[w]In patients with disease progression, the selection of TKI is based on prior therapy and/or mutational testing. Some data exist regarding the efficacy of second-generation TKIs against specific mutations. See Management of Cytogenetic or Hematologic Resistance to TKIs (CML-7).
[x]Imatinib 600 mg is the only FDA-approved TKI for patients with de novo accelerated phase. Nilotinib and dasatinib are also options for de novo accelerated phase. All other TKIs are approved for patients with disease progression due to resistance or intolerance to prior TKI therapy.
[y]Consider CNS prophylaxis/treatment.

*Available online, in these guidelines, at NCCN.org.

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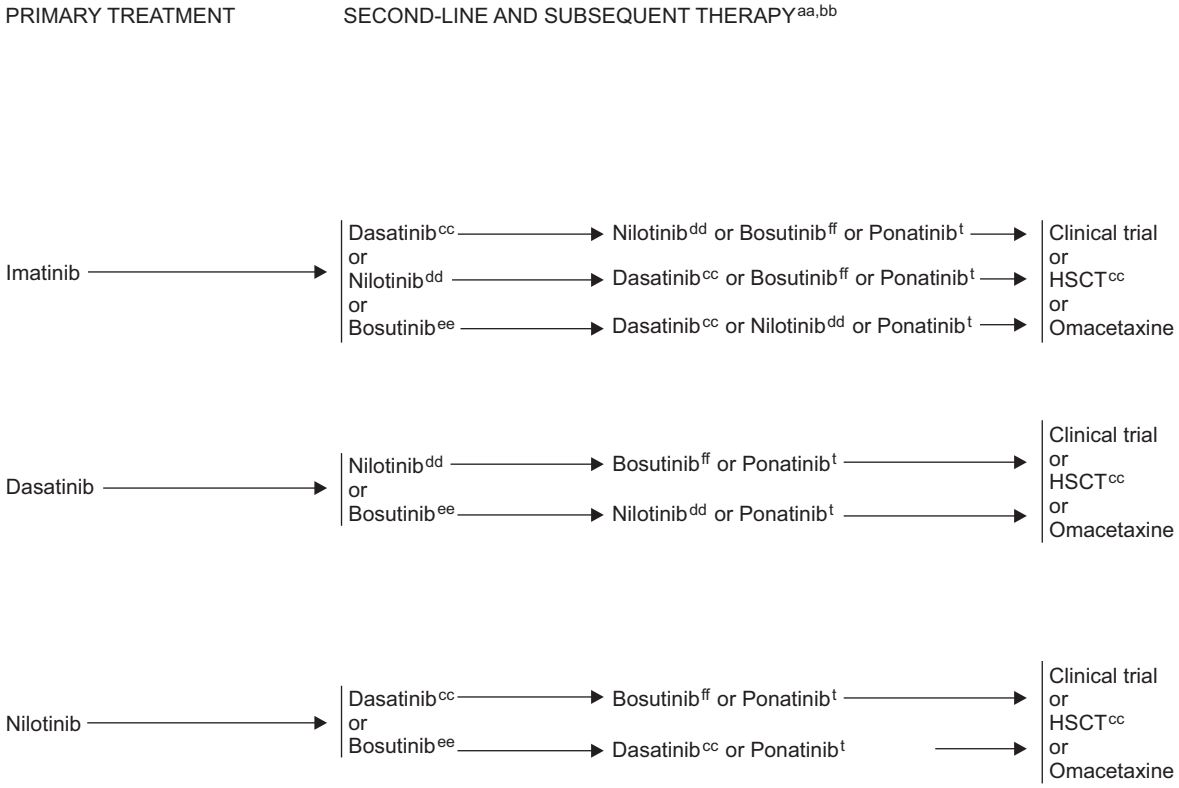
MANAGEMENT OF CYTOGENETIC OR HEMATOLOGIC RESISTANCE TO TKIs[z]



[t]Ponatinib is a treatment option for patients with a T315I mutation or who have not responded to 2 or more TKI therapies. See Management of Ponatinib Toxicity (CML-I; available online, in these guidelines, at NCCN.org).
[z]Patients with resistance to first-line imatinib should be treated with nilotinib, dasatinib, or bosutinib in the second-line setting. Patients with resistance to first-line nilotinib or dasatinib could be treated with an alternate TKI (other than imatinib) in the second-line setting.
[aa]Consider clinical trial, ponatinib, omacetaxine, or HSCT for patients with a T315I mutation.
[bb]Consider evaluation for HSCT depending on response to TKI therapy.
[cc]For patients with mutations Y253H, E255K/V or F359V/C/I.
[dd]For patients with mutations F317L/V/I/C, T315A or V299L.
[ee]For patients with mutations E255K/V, F317L/V/I/C, F359V/C/I, T315A or Y253H.

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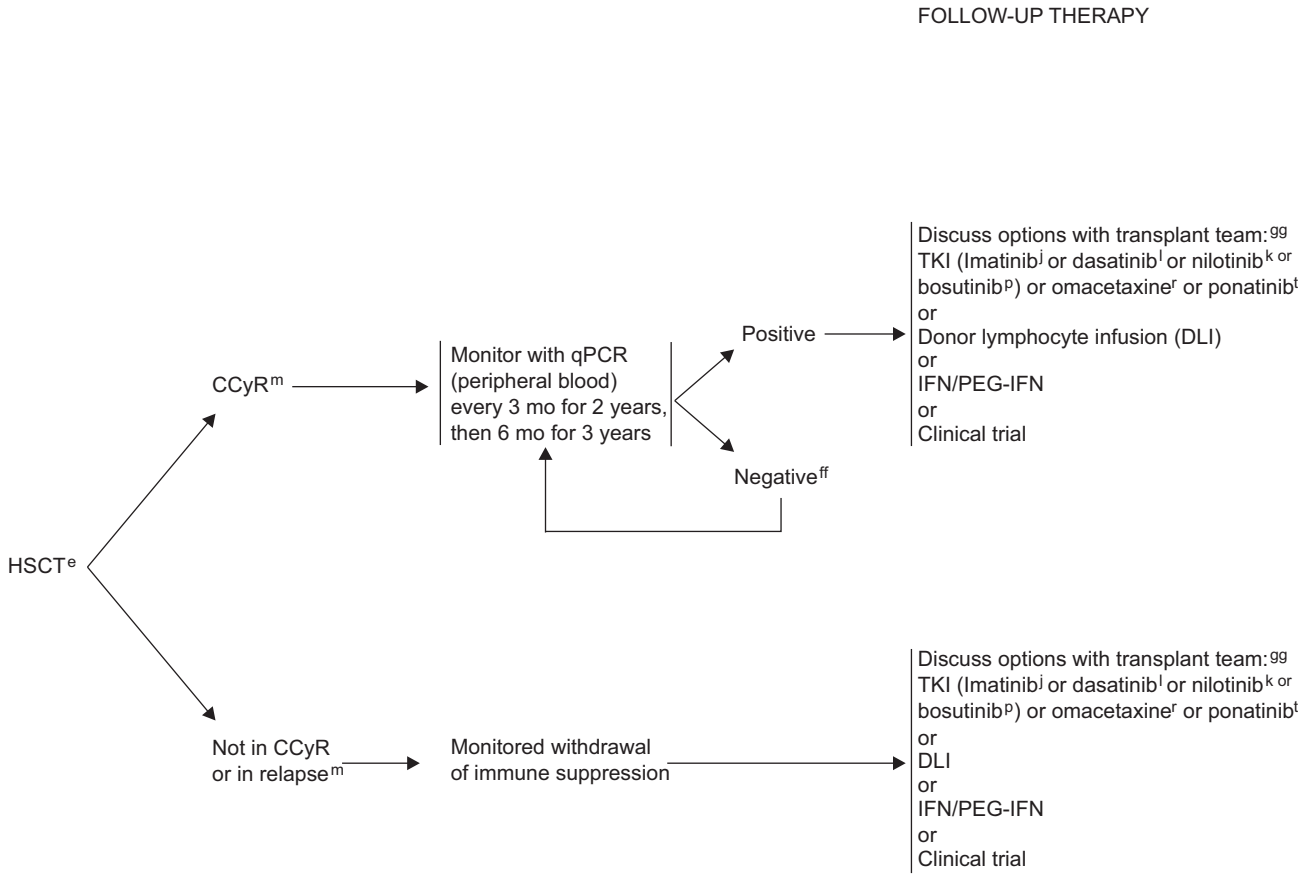

[e] Indications and outcomes of allogeneic HSCT are dependent on age, donor type, and transplant center. Nonmyeloablative HSCT is under investigation and should be performed only in the context of a clinical trial.
[j] See Management of Imatinib Toxicity (CML-D*).
[k] See Management of Nilotinib Toxicity (CML-E*).
[l] See Management of Dasatinib Toxicity (CML-F*).
[m] See Criteria for Hematologic, Cytogenetic, and Molecular Response and Relapse (CML-J).
[p] See Management of Bosutinib Toxicity (CML-G*).
[r] Omacetaxine is a treatment option for patients with resistance and/or intolerance to ≥2 TKIs. See Management of Omacetaxine Toxicity (CML-H*).
[t] Ponatinib is a treatment option for patients with a T315I mutation or disease that has not responded to 2 TKI therapies. See Management of Ponatinib Toxicity (CML-I*).
[ff] In patients with prior accelerated or blast phase, consider TKI therapy post HSCT for at least 1 year.
[gg] Data support the use of posttransplant imatinib but not in patients who have previously failed imatinib. Other TKIs may be more appropriate. Limited data are available on the use of dasatinib and nilotinib in a small number of patients with posttransplant relapse. No data support the use of bosutinib or omacetaxine for patients posttransplant. In patients who have disease that has failed to respond to prior TKI therapy, see CML-7 for the selection of posttransplant TKI.

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RISK CALCULATION TABLE

Study	Calculation	Risk Definition by Calculation
Sokal et al, 1984[1]	Exp 0.0116 x (age in years - 43.4) + (spleen - 7.51) + 0.188 x [(platelet count ÷ 700)^2 - 0.563] + 0.0887 x (blast cells - 2.10)	Low <0.8 Intermediate 0.8-1.2 High >1.2
Hasford et al, 1998[2]	0.666 when age ≥50 years + (0.042 x spleen) + 1.0956 when platelet count > 1500 x 10^9/L + (0.0584 x blast cells) + 0.20399 when basophils >3% + (0.0413 x eosinophils) x 100	Low ≤780 Intermediate 781-1480 High >1480

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

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[1] Sokal J, Cox E, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789-799.
[2] Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. J Natl Cancer Inst 1998;90:850-858.

CML-B

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DEFINITIONS OF ACCELERATED PHASE[1,2]

Modified Criteria Used at MD Anderson Cancer Center[3,4] (most commonly used in clinical trials)	World Health Organization (WHO) Criteria[5] (most commonly used by pathologists)
• Peripheral blood blasts ≥15% and <30% • Peripheral blood blasts and promyelocytes ≥30% • Peripheral blood basophils ≥20% • Platelet count ≤100 x 10^9/L unrelated to therapy • Clonal evolution	• Blasts 10%-19% of WBCs in peripheral and/or nucleated bone marrow cells • Peripheral blood basophils ≥20% • Persistent thrombocytopenia (<100 x 10^9/L) unrelated to therapy, or persistent thrombocytosis (>1000 x 10^9/L) unresponsive to therapy • Increasing spleen size and increasing WBC count unresponsive to therapy • Cytogenetic evidence of clonal evolution

[1]The table refers to myeloblasts. Any increase in lymphoblasts is concerning for (nascent) blast crisis.
[2]Sokal criteria (Sokal JE, Baccarani M, Russo D, et al. Staging and prognosis in chronic myelogenous leukemia. Semin Hematol 1988;25:49–61) and IBMTR criteria (Savage DG, Szydlo RM, Chase A, et al. Bone marrow transplantation for chronic myeloid leukemia: the effects of differing criteria for defining chronic phase on probabilities of survival and relapse. Br J Haematol 1997;99:30–35) are historically used when HSCT is the recommended treatment option.
[3]Kantarjian HM, Deisseroth A, Kurzrock R, et al. Chronic myelogenous leukemia: a concise update. Blood 1993;82:690–703.
[4]Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. Blood 2002;99:1928–1937.
[5]Adapted from Swerdlow SH, Campo E, Harris NJ, et al (Eds): World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press: Lyon 2008.

DEFINITIONS OF BLAST CRISIS

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

[1]Adapted from Swerdlow SH, Campo E, Harris NL, et al. WHO classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC; 2008.
[2]Druker BJ. Chronic Myelogenous Leukemia In: DeVita VT, Lawrence TS, Rosenburg SA, eds. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. Vol. 2 (ed 8): Lippincott, Williams and Wilkins; 2007:2267-2304

CML-K
CML-L

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Text cont. from page 1591.

definition is the WHO criteria, which defines accelerated phase as the presence of any of the following features: 10% to 19% of blasts in the peripheral blood or bone marrow, 20% or more of basophils in the peripheral blood, 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.[13] Cortes et al[12] suggested a modification to the WHO criteria (≥10%–29% peripheral blood or bone marrow blasts, ≥30% or more peripheral blood blasts and promyelocytes, ≥20% peripheral blood or bone marrow basophils, platelet count ≤100 x 10^9/L unrelated to therapy, and clonal evolution). It should be noted that clinical trials of tyrosine kinase inhibitors (TKIs) have largely reported efficacy data using the modified MD Anderson Cancer Center accelerated phase criteria (15% and <30% peripheral blood or bone marrow blasts, ≥30% or more peripheral blood blasts and promyelocytes, ≥20% peripheral blood or bone marrow basophils, platelet count ≤100 x 10^9/L unrelated to therapy, and clonal evolution).[11]

Blast Phase

Approximately 50% of all the blast phase cases are of the myeloid subtype, 25% are of the lymphoid subtype, and the remainder are undifferentiated. 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 (see CML-L, page 1597).[14] The WHO criteria defines blast crisis as 20% or greater blast cells in the peripheral blood or bone marrow, the presence of extramedullary blast proliferation, and large foci or clusters of blasts in the bone marrow biopsy (see CML-L, page 1597).[13]

Workup

Initial evaluation of patients should include a history and physical (H&P), including palpation of the spleen, CBC with differential, chemistry profile, bone marrow aspirate, and biopsy (see CML-1; page 1592).

Bone marrow cytogenetics and measurement of *BCR-ABL1* transcript levels using quantitative reverse transcriptase–polymerase chain reaction (qPCR) is recommended before initiation of treatment and for monitoring response to therapy.[15] Bone marrow cytogenetics not only provides morphologic review but also detects chromosomal abnormalities other than the Ph chromosome that are not detectable using peripheral blood. *BCR-ABL1* transcripts in the peripheral blood at very low levels (1–10 per 10^8 peripheral blood leukocytes) can also be detected in approximately 30% of normal individuals.[16,17] In addition, the incidence of *BCR-ABL1* transcripts in healthy individuals has also been shown to increase with advancing age.[16] TKI therapy would not be warranted, because most of these individuals would not develop CML.

The guidelines emphasize that conventional bone marrow cytogenetics should be performed to confirm the diagnosis of Ph+ CML at initial workup. If the collection of bone marrow is not feasible, fluorescence in situ hybridization (FISH) on a peripheral blood specimen with dual probes for *BCR* and *ABL1* genes is an acceptable method to confirm the diagnosis of CML.

The guidelines recommend determination of risk score and HLA antigen testing as part of initial workup (see CML-1, page 1592). The 2 prognostic scoring systems by Sokal et al[18] and Hasford et al[19] can be used to risk stratify patients with CML (see CML-B, page 1596). Both of these scoring systems stratify patients into 3 risk groups (low, intermediate, and high) and have been used in clinical trials evaluating TKIs. The Sokal score is based on the patient's age, spleen size, platelet count, and percentage of blasts in the peripheral blood.[18] The Hasford model includes eosinophils and basophils in the peripheral blood in addition to the same clinical variables used in the Sokal model.[19]

Patients with *BCR-ABL1*–positive CML (using bone marrow cytogenetics, FISH, or qPCR) are the focus of the NCCN Guidelines for CML. Patients who are *BCR-ABL1*–negative do not have CML. Patients who clearly do not have a myeloproliferative neoplasm (MPN; polycythemia vera, essential thrombocythemia, and primary myelofibrosis), have clinical features suggestive of CML, but do not have *BCR-ABL1* may have a so-called Ph-negative or atypical CML, and have a significantly worse prognosis than those with *BCR-ABL1*–positive CML.[20]

In ambiguous cases of *BCR-ABL1*–negative MPNs, further mutational analysis may help document clonality and define the entity. For example, mutations involving multiple genes, such as *JAK2*,

MPL, *CALR*, *TET2*, *ASXL1*, *CBL*, *EZH2*, *IDH*, *DNMT3A*, *LNK*, *RAS*, and *IKZF1*, have been described in *BCR-ABL1*–negative MPNs.[21–27] More recently, activating mutations in the *CSF3R* and *SETBP1* genes have been identified in chronic neutrophilic leukemia and atypical CML (Ph–negative).[28,29] Abnormalities in *FGFR1*, *PDGFRA*, and *PDGFRB* genes have been reported in a subset of patients with atypical MPNs that are usually associated with eosinophilia.[30]

Treatment Options

TKI Therapy: Imatinib has induced favorable hematologic and cytogenetic response rates in patients with AP-CML or BP-CML.[11,31–38] Dasatinib,[38–41] nilotinib,[38,42,43] bosutinib,[44] and ponatinib[45,46] have shown clinical activity in patients imatinib-resistant or imatinib-intolerant AP-CML or BP-CML.

The START-A trial evaluated the safety and efficacy of dasatinib (70 mg twice daily) in patients with AP-CML intolerant to imatinib or those with resistant disease.[40,47] At 8-month follow-up (for the first 107 patients enrolled in the study), a major hematologic response (MaHR) was achieved in 64% of patients, a major cytogenetic response (MCyR) was achieved in 33%, and 76% of patients remained progression-free.[47] Follow-up data from the full patient cohort of 174 patients confirmed the efficacy and safety of dasatinib in patients with AP-CML intolerant to imatinib or those with resistant disease.[40] The 12-month progression-free (PFS) and overall survival (OS) rates were 66% and 82%, respectively. The efficacy of dasatinib in patients with CML in myeloid blast crisis (MBC) or lymphoid blast crisis (LBC) intolerant to imatinib or those with resistant disease was evaluated in the START-B and START-L trials, respectively.[48] In patients with MBC-CML, 32% had achieved MaHR at 6-month follow-up, which increased to 34% at 8-month follow-up and was maintained at 12-month follow-up.[39] MCyR was achieved in 31% of patients. In the LBC-CML group, 31% achieved MaHR at 6-month follow-up, and this rate increased to 35% at 12-month follow-up.[39] After a minimum follow-up of 12 months, MCyR was achieved in 33% (MBC-CML) and 52% (LBC-CML) of patients, and complete cytogenetic response (CCyR) was achieved in 26% and 46% of patients, respectively. Median PFS and OS for patients with MBC were 6.7 and 11.8 months, respectively. In patients with LBC, the corresponding survival rates were 3.0 and 5.3 months, respectively.[39] Kantarjian et al[41] 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 in patients with AP-CML. Recently, 2-year follow-up data from a phase III trial showed that dasatinib, 140 mg once daily demonstrates equivalent efficacy and improved safety compared with 70 mg twice daily in patients with BP-CML.[49]

A phase II open-label trial evaluated the safety and efficacy of nilotinib (400 mg twice daily) in patients with AP-CML (n=119).[50] The efficacy end point for CP-CML was MCyR and the end point for AP-CML was MaHR. In patients with AP-CML, hematologic response was observed in 47% of patients and MCyR was observed in 29%.[50] The OS rate among the 119 patients after 12 months of follow-up was 79%. Nonhematologic adverse events were mostly mild to moderate. Grade 3 or higher bilirubin and lipase elevations occurred in 9% and 18% of patients. Long-term follow-up results confirmed that nilotinib induces rapid and durable responses with a favorable risk/benefit profile in patients with AP-CML who were intolerant or resistant to prior imatinib treatment.[42] Among patients with at least 24-month follow-up (n=137), a confirmed hematologic response was observed in 55% of patients and 31% had a complete hematologic response (CHR; 30% of patients with AP-CML resistant to imatinib and 37% of those intolerant to imatinib experienced a CHR). MCyR and CCyR were achieved in 32% and 20% of patients, respectively. Cytogenetic and molecular responses were also durable, with 66% of patients maintaining an MCyR at 24 months and 83% maintaining a CCyR at 12 months. The estimated PFS and OS rates at 24 months were 70% and 33%, respectively.[42] Nilotinib has also been evaluated in patients with BP-CML. In a phase II study of 136 patients with MBC (n=105) and LBC (n=31), after a minimum follow-up of 24 months, an MaHR was observed in 60% and 59% of patients, respectively.[43] An MCyR was achieved in 38% of patients with MBC and 52% of patients with LBC. A CCyR was seen in 30% of patients with MBC and 32% of patients with LBC. The OS rate was 42% at 12 months and 27% at 24 months. However, the responses were not durable. The duration of MCyR was 11 months for patients with MBC and 3 months for those with LBC.

The safety and efficacy of bosutinib (500 mg once daily) in patients with AP-CML or BP-CML was evaluated in a single-arm multicenter phase I–II trial. In the cohort of patients with AP-CML (n=63) and BP-CML (n=48), bosutinib induced CHR and MCyR in patients with and without *BCR-ABL1* mutations.[44] Among patients with AP-CML evaluable for response, CHR, MCyR, and CCyR were observed in 61% (20 of 33), 48% (13 of 27), and 33% (9 of 27) of patients, respectively. The corresponding response rates in patients with BP-CML evaluable for response were 32% (7 of 22), 52% (11 of 22), and 29% (6 of 22), respectively. Median follow-up for the entire cohort was 8.3 months.

A single-arm, multicenter, phase II trial (PACE trial) evaluated the safety and efficacy of ponatinib (45 mg once daily) in a total of 449 patients with CML intolerant to prior TKI therapy or those with resistant disease (dasatinib or nilotinib) or the T315I mutation (270 patients with CP-CML; 85 patients with AP-CML; 62 patients with BP-CML; 32 patients with Ph+ ALL).[45] The primary endpoint was MaHR at any time within 6 months after initiation of treatment for patients with advanced phase CML. The median follow-up was 15 months. Among patients with AP-CML intolerant to dasatinib or nilotinib or those with resistant disease, MaHR by 6 months was observed in 57% of patients. MCyR, CCyR, and major molecular response (MMR) rates were 34%, 22%, and 14%, respectively.[45] The corresponding response rates were 50%, 56%, 33%, and 22%, respectively, for patients with T315I mutation. The estimated PFS and OS rates at 12 months were 55% and 84%, respectively. Among patients with BP-CML intolerant to dasatinib or nilotinib or those with resistant disease, MaHR, MCyR, and CCyR were observed in 32%, 18%, and 16%, respectively.[45] The corresponding response rates were 29%, 29%, and 21%, respectively, for patients with T315I mutation. The estimated PFS and OS rates at 12 months were 19% and 29%, respectively. Longer-term follow-up data also confirmed the activity of ponatinib in patients with AP-CML and BP- CML; the 2-year OS rates were 72% and 18%, respectively, for patients with AP-CML and BP-CML.[46]

TKI Therapy and Toxicity: Chronic fatigue (mostly correlated with musculoskeletal pain and muscular cramps) was identified as a major factor limiting health-related quality of life in patients with CML treated with imatinib.[51] Hypophosphatemia (with associated changes in bone and mineral metabolism)[52] and decrease in bone mineral density have been noted in a small group of patients, suggesting that ongoing management of patients taking imatinib should include monitoring of bone health.[53] Congestive heart failure is uncommon among patients receiving imatinib, and its incidence rates are similar to those that occur in the general population. Patients with previous cardiac history should be monitored carefully. Aggressive medical therapy is recommended for symptomatic patients. Electrocardiogram should be considered for patients taking QT interval–prolonging medication.

Pleural effusion can be an adverse effect of dasatinib.[54,55] Close monitoring and timely intervention are necessary for patients at risk of developing pleural effusion. Reversible pulmonary arterial hypertension has been reported as a rare but serious side effect associated with dasatinib.[56–61] Evaluation for signs and symptoms of underlying cardiopulmonary disease before initiating and during treatment with dasatinib is recommended. If pulmonary arterial hypertension is confirmed, dasatinib should be permanently discontinued.

QT interval prolongation is a nonhematologic adverse reaction associated with nilotinib, which could be managed with dose reduction. Nilotinib labeling contains a black box warning regarding the risk of QT interval prolongation, and sudden cardiac death has been reported in patients receiving nilotinib. Electrolyte abnormalities should be corrected before nilotinib is initiated and should be monitored periodically. Drugs that prolong QT interval should be avoided. Electrocardiogram should be obtained to monitor the QT interval at baseline, 7 days after initiation of nilotinib, and periodically thereafter, and after any dose adjustments. Nilotinib may be associated with an increased risk of vascular adverse events, including peripheral arterial occlusive disease (PAOD).[62–64] Patients should be evaluated for preexisting PAOD and vascular risk factors before initiation of and during nilotinib treatment. If PAOD is confirmed, nilotinib should be permanently discontinued.

Bosutinib was also associated with minimal effects on QTc interval prolongation and a low incidence of pleural effusions, muscle cramps, musculoskeletal events, and cardiac toxicities that may be seen with other TKIs.

Hepatotoxicity, liver failure, and death have been rarely reported in patients treated with ponatinib. Liver function tests should be performed at baseline and at least monthly or as clinically indicated during treatment. Dose interruption and dose reductions or discontinuation of ponatinib should be considered for hepatotoxicity. Serious arterial thrombotic events were observed in 9% of patients (cardiovascular events, 5.1%; cerebrovascular events, 2.4%; and peripheral vascular events, 2.0%) and these events were considered to be treatment-related in 3% of patients (cardiovascular, cerebrovascular, and peripheral vascular events occurred in 2.0%, 0.4%, and 0.4% of patients, respectively).[45]

Based on the results of the PACE trial, the FDA approved ponatinib for the treatment of patients in all 3 phases of CML who were intolerant to prior TKI therapy or those with resistant disease. However, the recent Drug Safety Communication issued by the FDA on October 31, 2013 revealed an increase in the cumulative incidence of serious arterial thrombotic events.[65] Serious arterial and venous thrombosis and occlusions occurred in approximately 27% of patients: cardiovascular occlusion, cerebrovascular occlusion, and peripheral arterial occlusive events occurred in 12%, 6%, and 8% of patients, respectively. Heart failure, including fatalities, occurred in 8% of patients. These adverse events were seen in patients with and without cardiovascular risk factors (eg, history of ischemia, hypertension, diabetes, or hyperlipidemia).[66]

Ponatinib is now indicated only for the treatment of patients with T315I and those for whom no other TKI therapy is indicated in all 3 phases of CML. Ponatinib labeling also contains a black box warning regarding vascular occlusion, heart failure and hepatotoxicity. Patients should be monitored for evidence of thromboembolism and vascular occlusion. Ponatinib should be interrupted or stopped immediately for vascular occlusion and new or worsening heart failure.

TKI Therapy and Conception

Imatinib has been shown to be teratogenic and embryotoxic in animal studies. Some reports in literature indicate that patients who receive imatinib at the time of conception may have normal pregnancies.[67–74] Dasatinib and nilotinib are known to cause embryonic or fetal toxicities in animals. Isolated reports can be found in the literature regarding the outcome of pregnancy in patients receiving dasatinib[75–77] or nilotinib.[78]

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

Chemotherapy

High-dose combination chemotherapy has been used in patients with AP-CML or BP-CML, resulting in response rates of 25% to 60%.[79–83] In a study of 48 patients with AP-CML or BP-CML, intensive chemotherapy induced hematologic and cytogenetic responses in 29% and 23% of patients, respectively; CHR was observed in 25% of patients with AP-CML and 33% of patients with BP-CML.[79] Among patients with BP-CML, ALL-type chemotherapy regimens are associated with higher response rates in patients with lymphoid BP-CML (49% vs <20% for other morphologies; $P<.001$); however, the responses are not durable.[80]

Recent studies have shown that the addition of TKI to chemotherapy improves outcome in patients with BP-CML or Ph+ ALL.[84–94] The efficacy of imatinib in combination with chemotherapy in myeloid BP-CML has been demonstrated in several small studies.[87–89,91] In one study involving 18 patients with AP-CML and 10 patients with myeloid BP-CML, the combination of imatinib and decitabine induced CHR and MCyR in 32% and 18% of patients, respectively.[87] Partial hematologic response and minor cytogenetic response was observed in 4% and 11% of patients, respectively. The hematologic response rate was higher in patients without BCR-ABL1 kinase mutations (53% vs 14% for those with mutations). The median duration of hematologic response was 18 weeks. In a pilot study of 19 patients with myeloid BP-CML, the combination of imatinib, low-dose cytarabine , and idarubicin induced CHR in 47% of patients, and 26% returned to CP-CML.[88] In a more recent study of 36 patients with myeloid BP-CML, the addition of imatinib to daunorubicin and cytarabine resulted in a hematologic response rate of 78% (CHR rate of 55.5%) with a median follow-up of 6 years.[91] Median OS was 16.0 months, and the

OS in patients with hematologic response was 35.4 months.

The use of imatinib or dasatinib in combination with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) has been shown to be effective for the treatment of patients with lymphoid BP-CML.[93,94] In a study of 34 patients with lymphoid BP-CML or relapsed Ph+ ALL, the addition of dasatinib to hyper-CVAD resulted in an overall response rate of 91%, with 71% achieving a complete response [CR] and 21% achieving a CR with incomplete platelet recovery); 84% of patients achieved a CCyR after 1 cycle of therapy,[93] and the overall CMR rate was 42% (35% achieved MMR). At a median follow-up of 37.5 months among patients with lymphoid BP-CML, the 3-year OS rate was 70%, with 68% remaining in CR at 3 years.[93] The efficacy of hyper-CVAD used in combination with imatinib or dasatinib for patients with BP-CML, particularly when followed by allogeneic hematopoietic stem cell transplant (HSCT), was also confirmed in a more recent report.[94] Among 42 patients with BP-CML, CHR, CCyR, and CMR were achieved in 90%, 58%, and 25% of patients, respectively. The median remission duration and median OS were 14 and 17 months, respectively. In multivariate analysis, the median remission duration was longer among HSCT recipients (P=.01), and the median OS was longer among HSCT recipients (P<.001) and patients treated with dasatinib (P=.07).[94]

Omacetaxine (homoharringtonine, a cephalotoxic alkaloid), a protein synthesis inhibitor, has shown activity in patients with disease progression to AP-CML or BP-CML after prior therapy with 2 or more TKIs.[95,96] The results of a pooled analysis of 51 patients with AP-CML and 44 patients with BP-CML enrolled in 2 phase II studies (CML-202 and CML-203) demonstrated that omacetaxine is a feasible treatment option for patients with advanced phase CML that had failed treatment with multiple TKIs and those with a T315I mutation.[96] The median follow-up was 16.0 months for patients with AP-CML and 3.5 months for patients with BP-CML. Among the 51 patients with AP-CML, MaHR, CHR, and minor cytogenetic response were achieved or maintained in 37%, 29%, and 11% of patients, respectively. The median duration of MaHR was 5.6 months.[96] MaHR rates were 55% and 58%, respectively, for patients with a history of T315I mutation and for those with confirmed T315I mutation at baseline. The overall median PFS and OS were 4.8 and 17.6 months, respectively. Among patients with a history of T315I mutation, the median PFS and OS were 5.9 and 18.7 months, respectively. Among the 44 patients with BP-CML, MaHR and CHR were achieved in 9% and 7% of patients, respectively.[96] The median duration of overall hematologic response was 1.7 months. The overall median PFS and OS in patients were 2.2 and 3.5 months, respectively. Among the subgroup of patients with a history of T315I mutation (n=21), the median PFS and OS were 1.9 and 3.5 months, respectively.[96] The most common grade 3/4 hematologic adverse events were thrombocytopenia (51% and 30%, respectively, for patients with AP-CML and BP-CML), anemia (39% and 21%), neutropenia (20% and 21%), and febrile neutropenia (14% and 18%).

Omacetaxine is approved for the treatment of patients with CP-CML or AP-CML who are intolerant to 2 or more TKIs or those with resistant disease not responding to prior treatment with 2 or more TKIs.

NCCN Recommendations: The guidelines strongly recommend that patients with advanced phase CML be treated in specialized centers. Participation in a clinical trial is recommended for all patients with AP-CML or BP-CML.

Imatinib, dasatinib, nilotinib, and bosutinib are appropriate options for patients with de novo AP-CML (see CML-6, page 1593). Allogeneic HSCT can be considered based on response to TKI therapy. Omacetaxine is a treatment option for patients with resistant disease and/or intolerance to 2 or more TKIs.

TKI therapy alone or in combination with chemotherapy followed by allogeneic HSCT (if feasible) is recommended for patients in myeloid or lymphoid blast phase (see CML-6, page 1593). ALL-type chemotherapy is recommended for patients with lymphoid BP-CML (see NCCN Guidelines for ALL, available online at NCCN.org). Acute myeloid leukemia–type chemotherapy is recommended for those with myeloid BP-CML (see NCCN Guidelines for Acute Myeloid Leukemia, available online at NCCN.org).

A significant portion of patients with AP-CML or BP-CML treated with dasatinib or nilotinib

achieve a MCyR but not a concomitant CHR because of persistent cytopenias.[97] Fava et al[97] reported that failure to achieve a CHR at the time of MCyR was associated with an inferior outcome. The 2-year survival rate was 37% compared with 77% for patients with MCyR and concomitant CHR, suggesting that patients with MCyR without a CHR should be considered for alternate treatment options.

In patients who experienced disease progression to AP-CML or BP-CML during prior TKI therapy, the selection of TKI is based on prior therapy and/or mutational analysis.[98–100] Dasatinib, nilotinib, and bosutinib are active against many of the imatinib-resistant BCR-ABL1 kinase domain mutations, except T315I. Available clinical evidence indicates that in addition to T315I, mutations F317 and V299 are resistant to dasatinib, and mutations Y253H, E255, and F359 are resistant to nilotinib.[101,102] Bosutinib has shown potent activity in patients with *BCR-ABL1* mutations resistant to dasatinib (F317L) and nilotinib (Y253H and F359C/I/V).[103] Ponatinib has demonstrated activity in patients with E255K/V, F317L, F359V, G250E, M351T, T315I, and Y253H mutations.[104,105]

See CML-7 (page 1594) for the management of hematologic and cytogenetic resistance to TKI therapy. Mutational analysis is recommended before initiation of treatment for patients with AP-CML and BP-CML who have received prior TKI therapy.

Allogeneic Hematopoietic Stem Cell Transplant

Allogeneic HSCT is a potentially curative treatment for patients with CML, but the excellent results with TKI therapy have challenged the role of allogeneic HSCT as a first-line therapy.[106,107] The widespread application of allogeneic HSCT is limited by donor availability and the high toxicity of the procedure in older patients, which limits the age of eligibility at many centers to younger than 65 years. Ongoing advances in alternative donor sources (such as unrelated donors and cord blood), more accurate HLA typing of unrelated donors, and less toxic regimens are broadening the use of allogeneic HSCT. Transplants from unrelated matched donors can now be used for many patients with CML. The advent of molecular DNA assessment of HLA typing has enabled a rigorous and stringent selection of unrelated matched donors, and this improvement in typing has translated into greatly improved transplant outcomes, so that results with unrelated, fully matched donors are comparable to those of related matched donors.[108–110]

Investigational approaches using nonmyeloablative, reduced-intensity conditioning has been pioneered to engender a graft-versus-leukemia effect without exposing the patient to the toxicity associated with the myeloablative preparative regimen.[111-118] These studies are still investigational but are promising and show that molecular remissions may be achieved with nonmyeloablative, reduced-intensity conditioning in patients with CML.

Indications for Allogeneic HSCT

Allogeneic HSCT is an appropriate first-line treatment option for the rare patients presenting with BP-CML at diagnosis, patients with T315I and other *BCR-ABL1* mutations that are resistant to all TKIs, and rare patients who are intolerant to all TKIs.[106,119] A recent report from MD Andersen Cancer Center indicated that allogeneic HSCT is an effective strategy for patients with CML with T315I mutation, particularly in earlier stages; patients who underwent transplant in CP-CML had the best outcome.[120] In a more recent analysis of patients with CML resistant to imatinib (chronic phase, n=34; accelerated phase, n=9; and blast phase, n=4) who underwent HSCT at MD Anderson Cancer Center, the overall response rate was 89% and 68% of patients had an MMR.[121] The 2-year event-free survival rate was 36% for patients with *BCR-ABL1* mutations and 58% for those with no mutations. The corresponding 2-year OS rate was 44% and 76%, respectively. Nicolini et al[122] reported similar findings in 64 patients with *T315I* mutations. At a median follow-up of 26 months, survival probabilities at 24 months after allogeneic HSCT were 59%, 67%, and 30% for patients with CP-CML, AP-CML, and BP-CML, respectively. In multivariate analysis, blast phase at the time of transplant and transplants from unrelated donors were identified as adverse prognostic factors for OS.

Monitoring Response After Allogeneic HSCT

BCR-ABL1 transcripts persist after many years in most patients after allogeneic HSCT. Several studies have investigated the clinical significance of monitoring *BCR-ABL1* transcript levels with qPCR after HSCT.[123–128] Radich et al[125] reported that PCR positivity 6 or 12 months after HSCT is associated with

a higher risk of disease relapse (42%) compared with only 3% in patients who had negative PCR results. This study also showed that early PCR positivity is associated with more aggressive disease and a high risk of relapse. Olavarria et al,[127] who performed qPCR at 3 to 5 months after allogeneic HSCT, reported similar findings. At 3 years after allogeneic HSCT, the cumulative relapse rate was 17% for patients with no evidence of *BCR-ABL1* transcripts, 43% for those who had less than 100 *BCR-ABL1* transcripts, and 86% for those with more than 100 *BCR-ABL1* transcripts. PCR positivity at 6 months or less was also highly predictive of relapse in patients who received a T-cell–depleted transplant.[126] The prognostic significance of *BCR-ABL1* positivity is less evident after a longer period following transplantation. Costello et al[129] reported that the relapse rate was only 8% in patients with positive PCR results at more than 36 months after HSCT. Other investigators have reported that *BCR-ABL1* transcripts persist even in patients who are in CR for more than 10 years after HSCT.[130] More recently, Radich et al[128] analyzed 379 consecutive patients with CML alive at 18 months or more after HSCT to assess the relapse risk associated with *BCR-ABL1* detection in "late" CML survivors. Of 379 patients, 90 (24%) had at least 1 positive *BCR-ABL1* test 18 months after transplantation or later; 13 of 90 *BCR-ABL1*–positive patients (14%) and 3 of 289 *BCR-ABL1*–negative patients (1.0%) experienced relapse.

Thus, the prognostic significance of *BCR-ABL1* positivity is influenced by the time of testing after allogeneic HSCT. Although qPCR assay positive for *BCR-ABL1* at 6 to 12 months after transplant is associated with a high risk of relapse, a positive QPCR assay at a much later time point after transplant is associated with a lower risk of relapse. Early detection of *BCR-ABL1* transcripts after transplant may be useful to identify patients who may be in need of alternative therapies before the onset of a complete relapse.

Management of Posttransplant Relapse

Donor lymphocyte infusion (DLI) is effective in inducing durable molecular remissions in most patients with relapsed CML after allogeneic HSCT, although it is more effective in patients with chronic phase relapse than those with advanced phase relapse.[131–134] The probability of survival at 3 years after DLI was significantly better for patients who achieved molecular remission than for those who did not (95% and 53%, respectively; *P*=.0001).[132] However, DLI is associated with complications such as graft-versus-host disease (GVHD), susceptibility to infections, and immunosuppression.[131] Improvements in the methods of detecting *BCR-ABL1* transcripts to predict relapse, the development of reduced-intensity conditioning regimens, modified delivery of lymphocytes with the depletion of CD8+ cells, the use of escalating cell dosage regimens, and very-low-dose DLI in combination with interferon-alpha have reduced the incidence of GVHD associated with DLI.[135–139]

Imatinib has also been very effective in inducing durable remissions in most patients experiencing relapse in all phases of CML after allogeneic HSCT.[140–145] CHR and CCyR rates with posttransplant imatinib are higher in patients with chronic-phase relapse than in those with advanced-phase relapse. More recent studies have also reported durable molecular responses with imatinib in patients experiencing relapse of chronic and advanced phase disease.[146,147] Imatinib has also been shown to be effective in the prophylactic setting to prevent relapse after HSCT in high-risk patients. In a prospective evaluation of patients with Ph+ ALL (n=15) or CML beyond first chronic phase (n=7) in remission after myeloablative allogeneic HSCT, Carpenter et al[148] showed that imatinib can be safely administered during the first 90 days after myeloablative allogeneic HSCT at a dose intensity comparable to that used in primary therapy. Imatinib was administered for 1 year after HSCT. At a median follow-up of 1.4 years, most patients (CML, n=5; ALL, n=12) were in molecular remission. Olavarria et al[149] reported similar findings in patients undergoing reduced-intensity allogeneic HSCT in first chronic phase.

In a recent retrospective analysis, disease-free survival was significantly higher in patients receiving DLI than in those treated with imatinib.[150] A trend was also seen toward higher rates of complete molecular remissions in the DLI group. Some investigators have suggested that the combination of DLI and imatinib may be more effective at inducing rapid molecular remissions than either modality alone.[151] These observations are yet to be confirmed in randomized trials.

NCCN Recommendations: Allogeneic HSCT should be considered for patients with AP-CML or BP-CML. In patients with disease progression to ac-

celerated or blast phase on prior TKI therapy, treatment with a course of alternate TKI (not received before) will be beneficial as a bridge to allogeneic HSCT.

Patients who are in CCyR (qPCR-negative) should undergo regular qPCR monitoring (every 3 months for 2 years, then every 6 months for 3 years). Given the high risk for hematologic relapse in patients with prior AP-CML or BP-CML, posttransplant TKI therapy should be considered for at least 1 year in patients in remission after allogeneic HSCT (see CML-8; page 1595).[148]

A TKI (Imatinib, dasatinib, nilotinib, or bosutinib), omacetaxine, DLI, or interferon or pegylated interferon can be considered for patients who are not experiencing remission or cytogenetic relapse and those with an increasing level of molecular relapse. Monitored withdrawal of immune suppression is recommended before initiation of therapy for posttransplant relapse.

In patients with CML that has previously failed to respond to imatinib, no data support the use of posttransplant imatinib. Limited data in a small number of patients are available on the use of dasatinib and nilotinib in patients with posttransplant relapse.[152–156] Dasatinib may also be an effective treatment for extramedullary relapse after allogeneic HSCT.[157,158] No data support the use of posttransplant bosutinib, ponatinib, or omacetaxine.

Dasatinib, nilotinib, bosutinib, ponatinib, or omacetaxine may be more appropriate for patients with CML that has previously failed imatinib. Participation in a clinical trial should be considered.

Summary

TKI therapy (alone or in combination with chemotherapy) remains the standard initial treatment for patients with AP-CML. In patients with disease progression, selection of the appropriate TKI is based on previous therapy, the side-effect profile of the agent, and the TKI's relative effectiveness against *BCR-ABL1* mutations. Allogeneic HSCT should be considered for patients with AP-CML or BP-CML. Ongoing clinical trials are evaluating alternate treatment options for patients with *BCR-ABL1* mutations resistant to currently approved TKIs. Consistent with NCCN philosophy, participation in clinical trials is encouraged.

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Individual Disclosures of the NCCN Chronic Myelogenous Leukemia Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Camille N. Abboud, MD	Eli Lilly and Company; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; and Teva	Alexion Pharmaceuticals, Inc.; ARIAD Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; and Teva	None	None	5/8/14
Mojtaba Akhtari, MD	None	None	None	None	5/15/13
Jessica K. Altman, MD	ARIAD Pharmaceuticals, Inc.; Boehringer Ingelheim GmbH; Bristol-Myers Squibb Company; Millennium Pharmaceuticals, Inc.; Agios; Ambit; Astellas; Cyclacel; Epizyme; Lilly Pharmaceuticals; Talon; and Pfizer Inc.	Amgen Inc.; ARIAD Pharmaceuticals, Inc.; ARIAD Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; Celgene Corporation; and Genoptix	None	None	6/4/14
Ellin Berman, MD	ARIAD Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; and Ariad Pharmaceuticals	ARIAD Pharmaceuticals, Inc.	None	None	5/23/14
Peter Curtin, MD	Onconova	None	None	None	11/21/13
Daniel J. DeAngelo, MD, PhD	None	ARIAD Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; Novartis Pharmaceuticals Corporation; and Sigma-Tau Pharmaceuticals, Inc.	None	None	9/5/13
Michael Deininger, MD, PhD	ARIAD Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; Celgene Corporation; Novartis Pharmaceuticals Corporation; and Gilead	ARIAD Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	None	None	5/1/14
Steven Devine, MD	Genzyme Corporation	GlaxoSmithKline; Kiadis; and sanofi-aventis U.S.	None	None	5/22/14
Amir T. Fathi, MD	None	Agios Pharmaceuticals; Seattle Genetics; and Teva Pharmaceuticals	None	None	10/18/13
Jason Gotlib, MD, MS	None	Novartis Pharmaceuticals Corporation	None	None	3/21/14
Madan Jagasia, MD	None	Therakos, Inc.	None	None	6/5/14
Patricia Kropf, MD	None	Celgene Corporation; and Millennium Pharmaceuticals, Inc.	None	None	4/9/14
Joseph O. Moore, MD	ARIAD Pharmaceuticals, Inc.; Genentech, Inc.; and Novartis Pharmaceuticals Corporation	ARIAD Pharmaceuticals, Inc.; Genentech, Inc.; and Novartis Pharmaceuticals Corporation	None	None	1/15/14
Susan O'Brien, MD	Ariad; Infinity; and Morphosys	Teva	None	None	8/27/13
Arnel Pallera, MD	None	None	None	None	5/30/14
Jerald P. Radich, MD	Novartis Pharmaceuticals Corporation	ARIAD Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; Novartis Pharmaceuticals Corporation; Incyte; and Pfizer Inc.	None	None	5/30/14
Vishnu VB. Reddy, MD	None	None	None	None	10/18/13
Neil P. Shah, MD, PhD	ARIAD Pharmaceuticals, Inc.; and Bristol-Myers Squibb Company	None	None	None	10/22/13
B. Douglas Smith, MD	Bristol-Myers Squibb Company; Merck & Co., Inc.; CSL-Behring; and Pfizer Inc.	ARIAD Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; Novartis Pharmaceuticals Corporation; and Incyte	None	None	5/2/14
David S. Snyder, MD	Bristol-Myers Squibb Company; and Novartis Pharmaceuticals Corporation	ARIAD Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; and Novartis Pharmaceuticals Corporation	None	None	4/1/14
Meir Wetzler, MD	Bristol-Myers Squibb Company; NCI; Cyclacel; MedPace; OSU; and Prime Oncology	Boehringer Ingelheim GmbH; Clinical Connexion; Dava; Envision; Intellsphere; McVeigh; MedLearning; P4 Healthcare; Sigma-Tao; and WebMD	None	None	7/30/14

The NCCN guidelines staff have no conflicts to disclose.