

Current and Future Clinical Strategies in the Management of Chronic Myeloid Leukemia

Kamakshi V. Rao, Pharm.D., Andrea Iannucci, Pharm.D., and Elias Jabbour, M.D.

Rational design of tyrosine kinase inhibitors, such as imatinib, against leukemogenic Bcr-Abl kinase has resulted in unprecedented responses and survival rates in patients with chronic myeloid leukemia (CML). Although these responses are sustained for years in the majority of patients, a fraction of the patients either fail or respond suboptimally to imatinib therapy, or are intolerant to the drug. Biologic insights into the mechanisms of imatinib resistance led to the development of several strategies, including dose escalation and second-generation tyrosine kinase inhibitors. Dasatinib and nilotinib are second-generation tyrosine kinase inhibitors that are approved as second-line treatment for imatinib-resistant patients based on their activity in these patients and their favorable toxicity profiles. Dasatinib and nilotinib have demonstrated promising activity as front-line therapy and are being directly compared with imatinib therapy in this setting. Salvage treatment options are evolving for patients with CML, with several novel agents showing promising activity, even in patients with the noted T315I mutation. The role of stem cell transplantation for patients with CML is being redefined in the context of significant transplantation-related morbidity and mortality and the availability of effective alternate therapies. In this context, practical considerations such as guidelines for monitoring responses to imatinib therapy, criteria for choice of second-line therapy, management of the adverse events of tyrosine kinase inhibitors, and quality-of-life issues are of particular importance. This review summarizes recent advances in the treatment of CML over the past decade, with an emphasis on tyrosine kinase inhibitor therapy.

Key Words: chronic myelogenous leukemia, chronic myeloid leukemia, CML, tyrosine kinase inhibitor, TKI, imatinib, nilotinib, dasatinib, stem cell transplant, interferon, cytarabine, AP24534.

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Chronic myeloid leukemia (CML) is a myeloproliferative disorder resulting from clonal expansion of transformed hematopoietic progenitor

From the Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina (Dr. Rao); the University of California San Francisco School of Pharmacy, San Francisco, California, and the University of California Davis Medical Center, Davis, California (Dr. Iannucci); and the Department of Leukemia, The University of Texas, M. D. Anderson Cancer Center, Houston, Texas (Dr. Jabbour).

For reprints, visit <http://www.atypon-link.com/PPI/loi/phco>. For comments or questions, contact Elias Jabbour, M.D., Department of Leukemia, The University of Texas, M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Box 0428, Houston, TX 77030; e-mail: ejabbour@mdanderson.org.

cells.¹ Chronic myeloid leukemia accounts for about 15% of leukemia cases in adults, with approximately 5050 new cases of CML diagnosed and 470 deaths attributed to the disease in the United States in 2009.² The median age at diagnosis of CML is 55 years, with a third of all patients with CML older than 60 years.³ Chronic myeloid leukemia occurs more frequently in men than in women, with a male:female ratio of 1.3:1, and the incidence increases with age.^{2, 4}

Pathophysiology

A distinguishing feature of CML is the presence

of the Philadelphia (Ph, 22q-) chromosome, which is the consequence of a reciprocal translocation between chromosomes 9 and 22, t(9;22)(q11.2).⁵ This genetic abnormality creates an aberrant fusion gene, *BCR-ABL*, derived from the *ABL* gene on chromosome 9 and the breakpoint cluster region (BCR) on chromosome 22.^{6,7} The *BCR-ABL* fusion gene product results in a constitutively active protein tyrosine kinase, p210^{BCR-ABL}, which is critical for the pathogenesis of CML. Under normal physiologic conditions, ABL tyrosine kinase is tightly regulated and modulates a number of downstream molecular targets, including c-Myc, Akt, and Jun, all of which are essential for the proliferation and survival of normal cells. In contrast, the aberrant *BCR-ABL* tyrosine kinase provides a survival advantage to malignant cells by promoting uncontrolled cellular proliferation and survival in addition to altered adhesion properties.⁸⁻¹¹

The disease progression of CML occurs in three stages—chronic phase, accelerated phase, and blast crisis—based on pathology and clinical presentation. The chronic phase is a relatively indolent phase characterized by well-differentiated leukemic cells. Although the malignant cells have a slight growth advantage, they retain a nearly normal differentiation capacity as they have not yet become growth factor independent.¹¹⁻¹³ In chronic-phase CML, the white blood cell count might be elevated whereas neutrophil and platelet functions typically remain normal.¹¹ Often within 5 years of diagnosis, the chronic phase will be followed by progression to the intermediate accelerated phase or terminal blast crisis. The accelerated phase is defined by peripheral blood findings of marrow blasts of 5% or greater, basophils greater than 20%, or a platelet count of $1000 \times 10^3/\text{mm}^3$ or higher despite adequate therapy. Bone marrow abnormalities include karyotype evolution, frequent Pelger-Huet-like neutrophils, nucleated erythrocytes, megakaryocyte nuclear fragments, and marrow collagen fibrosis. Anemia or thrombocytopenia unrelated to therapy, progressive splenomegaly, leukocyte doubling time of less than 5 days, and fever not otherwise explained are clinical manifestations of accelerated-phase CML.⁴ The accelerated phase may last 3–18 months; however, approximately 25% of patients may transition directly from the chronic phase into blast crisis.^{4,14} The blast crisis phase, which resembles acute leukemia, is usually defined by the presence of extramedullary blastic infiltrates or 30% or more leukemic blasts in peripheral blood or marrow. Death usually

ensues within 3–6 months after a patient enters this final phase.⁴

Although the mechanistic basis of the transition from the chronic phase to advanced stages of CML is poorly understood, it is likely due to acquisition of additional genetic mutations by the genomically unstable *BCR-ABL*-containing malignant cells.¹¹ These mutations might arise in the *BCR-ABL* gene or in critical oncogenes and tumor-suppressor genes such as p53, Rb, and INK4, thus further increasing the oncogenic potential of CML cells. In addition, p210^{BCR-ABL} is implicated in impaired DNA repair and antiapoptotic mechanisms that would allow propagation of DNA errors in CML cells.^{4,11}

Clinical Presentation and Diagnosis of Chronic Myeloid Leukemia

Most patients (85%) are in the chronic phase when they are diagnosed with CML.⁴ Symptoms tend to be mild, and as many as 45% of patients are diagnosed after routine blood tests while still asymptomatic. Approximately 5% of patients are in the accelerated phase and 10% in blast crisis when diagnosed.⁴ Among those initially diagnosed in the chronic phase, the accelerated phase is heralded by worsening symptoms and increasing need for higher doses of drugs to control the disease.⁸ Persistent splenomegaly despite therapy also suggests disease acceleration.

Symptomatic patients may present with fatigue, malaise, bleeding, sweating, and weight loss. An enlarged spleen may cause feelings of early satiety and left upper quadrant pain or mass.^{4,8} Purpura and splenomegaly are often found on physical examination, and leukocytosis, anemia, and thrombocytosis are common laboratory findings.^{4,15} Hepatomegaly may occasionally be found. Lymphadenopathy and myeloid sarcomas are unusual in early CML but become more common late in the course of the disease and are associated with poor prognosis.⁸

A CML diagnostic workup includes a complete blood cell count with differential and platelet count, and bone marrow aspiration with measurement of the percentages of blasts and basophils. Bone marrow biopsy and cytogenetic studies are routinely assessed for Ph chromosome and karyotypic evolution markers.⁴

Almost all patients with CML will have increased bone marrow cellularity that will be primarily of myeloid and megakaryocytic lineages with a substantially altered myeloid:erythroid ratio at diagnosis.⁸ However, as most patients are in

chronic phase at diagnosis, the blast percentage is usually normal or only slightly elevated, but marrow or blood basophilia, eosinophilia, and monocytosis may be found. Cytogenetic analysis finds the t(9;22)(q34;q11.2) or Ph chromosome in approximately 90–95% of patients. A diagnosis of CML requires evidence of the translocation by cytogenetics, fluorescence in situ hybridization, or molecular techniques.

History of Chronic Myeloid Leukemia Therapy

The successful introduction of tyrosine kinase inhibitor therapy has revolutionized the management of CML. Before the advent of these agents, the median survival time for patients with CML was about 4 years.⁸ Historically, standard treatment for CML consisted of either the alkylating agent busulfan, or the ribonucleotide inhibitor hydroxyurea. Although both busulfan and hydroxyurea controlled the hematologic manifestations of CML, neither affected the clinical course of the disease. Busulfan and hydroxyurea therapy were associated with a median survival of 44 months and 56 months, respectively, in patients with chronic-phase CML.^{4, 16} Hydroxyurea also led to prolongation of the chronic phase compared with busulfan (47 mo vs 37 mo).^{4, 16} Busulfan therapy was associated with significant toxicities including severe and prolonged myelosuppression, which occurred in 10% of patients; idiosyncratic pulmonary reactions; marrow fibrosis; and endocardial fibrosis.^{4, 17} Hydroxyurea was associated with a more tolerable toxicity profile; rare adverse effects associated with hydroxyurea therapy included nausea, vomiting, diarrhea, mucosal ulcers, and skin problems.⁴ Although hydroxyurea is not included in the front-line treatment of CML in the current era of tyrosine kinase inhibitors, it is commonly used as a temporary measure, to control leukocytosis, before instituting standard therapy.^{4, 16}

Introduction of interferon- α (IFN- α) in the 1980s improved overall survival for patients and was the standard of care for CML until the advent of tyrosine kinase inhibitor therapy. Treatment with IFN- α yielded complete hematologic response in 50–80% of previously untreated patients with chronic-phase CML (Table 1).^{4, 18, 19} Cytogenetic responses were achieved in 40–60% of patients, including complete cytogenetic responses (defined as no detectable Ph chromosome in at least 20 bone marrow metaphases) in 5–25% of patients with chronic-phase CML.^{4, 20, 21} The results of a meta-analysis of randomized

Table 1. Response Rates for Interferon- α in Studies of Interferon- α vs Chemotherapy in Patients with Chronic Myeloid Leukemia^{14, 18–21}

Outcome	Response Rate
Complete hematologic response	50–80%
Major cytogenetic response	10–40%
Complete cytogenetic response	5–25%
5-year survival rate (interferon- α vs chemotherapy)	57% vs 42% ($p < 0.00001$)

studies comparing IFN- α and hydroxyurea or busulfan indicated that survival was better with IFN- α than with the chemotherapeutic agents. The 5-year survival rate for IFN- α was 57% compared with 42% for hydroxyurea and busulfan ($p < 0.00001$).²⁰ Additional benefits were achieved by combining IFN- α with cytarabine, and the probability of achieving a complete cytogenetic response was increased to as high as 35% with this combination.^{22, 23} The probability of survival in patients who achieved complete cytogenetic response with IFN- α therapy was 78% compared with 39% and 25% in those who achieved a partial cytogenetic response and minimal or no cytogenetic response, respectively, highlighting the prognostic importance of achieving complete cytogenetic response.²¹ Unfortunately, IFN- α has minimal activity in CML that is in the accelerated or blastic phases. In addition, IFN- α therapy is associated with significant adverse effects, including flu-like symptoms, fever, chills, myalgias, fatigue, depression, neuropathy, diarrhea, memory loss, immune-mediated complications, and myelosuppression.²⁴

The evidence from the IFN- α era highlighted the importance of achieving a complete cytogenetic response. Moreover, *BCR-ABL* transcripts as measured by polymerase chain reaction (PCR) were undetectable in nearly 30% of patients with a complete cytogenetic response.²¹ After a median follow-up of 10 years, none of these patients had relapsed and may, in fact, be cured.^{21, 25} It is also important to note that 40–60% of patients who achieved a complete cytogenetic response with the presence of minimal residual disease at the molecular level had not relapsed after 10 years.^{21, 25} Interferon- α -induced immune modulation, including the presence of cytotoxic T lymphocytes specific for P210, a peptide that is overexpressed in CML cells, is believed to be responsible for this phenomenon.²⁶

Current Front-Line Treatment Options

The treatment of CML changed dramatically

Table 2. The Sokal and Hasford Scoring Systems³⁹

Scoring System	Equation	Risk Category Score		
		Low	Intermediate	High
Sokal score	$e^{[0.0116 (\text{age in yrs} - 43.4) + 0.0345 (\text{spleen size in cm} - 7.51) + 0.188 (\text{platelet count}/700 \times 10^3/\text{mm}^3)^2 - 0.563] + 0.0887(\text{myeloblasts} [\%] - 2.1)}$	< 0.8	0.8–1.2	> 1.2
Hasford score	(0.666 if age \geq 50 yrs, otherwise 0) + (0.042 x spleen size in cm) + (1.0956 if platelet count > 1500 x 10 ³ /mm ³ , otherwise 0) + (0.0584 x myeloblasts [%]) + (0.20399 if basophils > 3%, otherwise 0) + (0.0413 x eosinophils [%]) x 100	\leq 780	781–1480	> 1480

with the advent of imatinib mesylate. Evaluation of this orally administered 2-phenylamino-pyrimidine derivative began in the late 1990s. Imatinib is a small-molecule tyrosine kinase inhibitor that binds to the adenosine triphosphate (ATP) binding site of the Abl enzyme in the inactive/closed conformation, causing P-loop folding over the ATP binding site and activation loop blockade of the substrate binding site. This prevents the phosphorylation of a critical residue necessary for substrate binding and kinase activity.²⁷ Besides Abl, imatinib also inhibits the kinase activities of several other tyrosine kinases including ABL-related, protein-tyrosine kinase gene (ARG), the class III family of receptor tyrosine kinases such as KIT, platelet-derived growth factor receptor (PDGFR), and the macrophage colony-stimulating factor receptor.^{28–32}

Imatinib Trial Evidence

Imatinib was initially investigated in patients with accelerated-phase, blast crisis, and late chronic-phase CML who were resistant to or intolerant to IFN- α therapy. Based on the encouraging results of these early trials, a prospective, randomized, phase III trial, known as the International Randomized Study of Interferon versus STI571 (IRIS), was initiated in 2000 to compare single-agent imatinib with IFN- α plus low-dose cytarabine therapy in treatment-naïve patients with early chronic-phase CML.^{33, 34} The results of the IRIS trial resulted in a fundamental change in the treatment of CML and established imatinib as front-line therapy.²⁷ Imatinib was the first tyrosine kinase inhibitor to be approved for the treatment of CML and is indicated as treatment of all phases of newly diagnosed CML.³⁵ Imatinib is also recommended as front-line therapy for chronic-phase CML by the National Comprehensive Cancer Network (NCCN)³⁶ and European LeukemiaNET (ELN).³⁷

The IRIS trial randomized 1106 patients with

newly diagnosed early chronic-phase CML to imatinib 400 mg/day or IFN- α at a target dose of 5 million U/m²/day plus cytarabine 20 mg/m²/day for 10 days every month.³³ After a median follow-up of 18 months, 95% of patients treated with imatinib achieved a complete hematologic response (defined by normal complete blood cell counts and differentials) compared with 56% of patients treated with IFN- α plus cytarabine ($p < 0.001$), whereas complete cytogenetic response was achieved in 68% and 5%, respectively ($p < 0.001$). The 12-month major molecular response (defined as reduction in *BCR-ABL* transcript levels by at least 3-log) rate was 40% for the imatinib group and 2% for the IFN- α group, which was possibly the most important finding of the study.³⁴

Five-year follow-up data from IRIS demonstrated the enduring efficacy and long-term safety of imatinib.³⁸ At a median follow-up of 60 months, only 7% of patients progressed to accelerated-phase or blast crisis CML, whereas the estimated overall survival of patients who had received imatinib as initial therapy was 89%; exclusion of deaths unrelated to CML resulted in a higher survival rate of 95%. Event-free survival at 60 months was 83%.

The IRIS study emphasized the importance of the level of treatment response to long-term outcomes. By 12 months, a major cytogenetic response had occurred in 85% and a complete cytogenetic response in 69% of patients treated with imatinib.³⁸ The estimated rates at 60 months were 92% and 87%, respectively. Cytogenetic response differed according to whether patients with CML were low risk, intermediate risk, or high risk according to the Sokal scoring system (Table 2).³⁹

A complete cytogenetic response was achieved by 89% of patients who were low risk, 82% of intermediate-risk patients, and 69% of those who were at high risk.³⁸ These differences were significant ($p < 0.001$), underscoring the importance of risk levels to response. Disease progression was

also significantly more likely to occur in patients at higher risk; however, this was not true in those patients who had complete cytogenetic or molecular responses, despite their Sokal risk scores. In patients who achieved a complete cytogenetic response and a reduction of at least 3-log in levels of *BCR-ABL* transcripts by 18 months, the estimated rate of survival without disease progression at 60 months was 100%. The probability of losing a response or progressing to accelerated or blastic phase decreases significantly over time, highlighting the importance of achieving an optimal response early in the course of therapy.

Recently, an 8-year update of IRIS demonstrated that treatment with imatinib maintained high response and event-free survival rates, as well as a low rate of progression to accelerated phase or blast crisis (Table 3).⁴⁰ Overall survival at 8 years was estimated to be 85%, and 55% of patients originally randomized to imatinib continued with treatment. Fifteen (3%) patients in the intent-to-treat population progressed to accelerated phase or blast crisis. Approximately 80% of patients who achieved partial cytogenetic response at 12 months improved their response to complete cytogenetic response. The 8-year major molecular response rate was 86%, and no patients with major molecular response at 12 months progressed to accelerated phase or blast crisis.

Initially, IRIS did not demonstrate a survival advantage for imatinib; however, this may have been the result of the crossover design and the fact that imatinib received accelerated approval while the study was still in its early stages. As a result of the latter event, many of the IFN- α -treated patients crossed over to the imatinib arm of the study.³⁸ Because imatinib induces responses in patients for whom previous IFN- α therapy failed, this might have obscured any survival benefit. However, the long-term data have shown a clear benefit for patients who were initiated with imatinib therapy. Taken into the context of benefits achieved in the past with IFN- α -based therapy, imatinib therapy is clearly superior in treating newly diagnosed CML.

Since it is unlikely that confirmatory prospective randomized trials of imatinib versus standard therapies will be performed, evidence confirming the long-term survival benefits of imatinib was extrapolated from retrospective studies. One such large retrospective analysis conducted by the M. D. Anderson Cancer Center compared imatinib 400 mg/day (73 patients) and imatinib

Table 3. 8-Year Follow-up of IRIS: Efficacy of Imatinib in 553 Newly Diagnosed Patients with Chronic-Phase Chronic Myeloid Leukemia⁴⁰

Efficacy Measure	Percentage of Patients
Cumulative complete cytogenetic response	83
8-yr event-free survival	81
8-yr freedom from progression to accelerated phase or blast crisis	92
8-yr overall survival	85
8-yr major molecular response	86

IRIS = International Randomized Study of Interferon versus STI571.

800 mg/day (194 patients) with IFN- α -based regimens (650 patients) in newly diagnosed patients with Ph chromosome-positive (Ph+) early chronic-phase CML.⁴¹ The estimated 5-year survival rate was significantly higher for patients treated with imatinib compared with those treated with IFN- α therapy (88% vs 63%, $p=0.001$). Results from patients treated with different doses of imatinib and IFN- α were consolidated since no survival differences were discerned when analyzed by dose. These results were consistent with those of another retrospective analysis that compared long-term survival rates of patients treated with imatinib in IRIS (551 patients) with those who had been treated with IFN- α plus cytarabine in the phase III CML91 trial (325 patients).⁴² Three-year survival was 92% for the imatinib treatment cohort compared with 84% for the IFN- α plus cytarabine group ($p<0.001$). In both of these trials, survival advantage with imatinib was also confirmed within different Sokal prognostic risk groups.

In order to determine if any survival advantage with imatinib extended to patients with more advanced disease, the survival outcomes of 176 patients with accelerated-phase CML was compared with 213 historical controls who received IFN- α or other agents, including decitabine or homoharringtonine.⁴³ The median survival time for patients with accelerated-phase CML receiving therapy other than imatinib was approximately 2 years; however, for patients treated with imatinib, the median survival time was not reached at 4 years (53%). At 4 years, the overall survival rate was 42% for IFN- α regimens and 0–21% for other regimens. Moreover, patients with accelerated-phase CML who underwent allogeneic stem cell transplantation (alloSCT) had an estimated 5-year survival of 25–30%. Nonetheless, it must be taken into account that much of the mortality associated with alloSCT occurs in the early posttransplantation period.

Table 4. Toxicities Associated with Tyrosine Kinase Inhibitor Therapy in Patients with Chronic Myeloid Leukemia^{33, 44-52}

Adverse Event	Percentage of Patients		
	Imatinib 400 mg/day	Dasatinib 100 mg/day	Nilotinib 800 mg/day
Neutropenia (grade 3 or 4)	17	35	31
Thrombocytopenia (grade 3 or 4)	9	23	30
Fluid retention (any grade)	62	34	11
Pleural effusion	< 7	18	NR
Superficial edema (any grade)	60	18	6
Rash (any grade)	34	17	33
Pruritis (any grade)	7	26	29
Musculoskeletal pain, muscle cramps (any grade)	47-49	19	11
Myalgia (any grade)	24	13	14
Fatigue (any grade)	39	24	28
Headache (any grade)	37	33	31
Diarrhea (any grade)	45	27	22
Nausea	50	18	31

NR = not reported.

Long-term Safety and Tolerability

The most common adverse events of any grade reported with imatinib therapy in IRIS included edema (60%), muscle cramps (49%), diarrhea (45%), nausea (50%), musculoskeletal pain (47%), and rash and skin problems (40%) (Table 4).^{33, 38, 44, 45} Fatigue, headache, abdominal pain, and joint pain were noted to occur in 39%, 37%, 37%, and 31% of patients, respectively. Grade 3 or 4 adverse events included neutropenia (17%), thrombocytopenia (9%), and anemia (4%). However, in most patients, myelosuppression was transient and occurred most often in the first 3 months of therapy. Furthermore, persistent or recurrent myelosuppression was manageable with hematopoietic growth factor support.⁵³⁻⁵⁵

A possible association of imatinib therapy with heart failure has also been reported, which might be causally linked to ABL inhibition. Of 1276 patients treated with imatinib at a single institution, 22 (1.7%) patients reported symptoms that could be attributed to heart failure.⁵⁶ Considering that the median age of patients with heart failure in the study was 70 years, only eight of the events were considered possibly or probably related to imatinib. Furthermore, 11 of the 22 patients who reported symptoms were able to continue receiving imatinib therapy with dosage adjustments and management of heart failure symptoms without further complication. Although there is no indication that patients receiving imatinib should undergo increased cardiac screening, these data do suggest that in

those who develop symptoms, the cause should be thoroughly investigated.

Intolerance to imatinib therapy due to drug toxicity is a major cause of discontinuation and poses a significant clinical issue. About 29% of patients who receive imatinib require dose interruption, and 26% of these patients go on to discontinue therapy. Intolerance is more frequently observed in patients in advanced stages of CML who have experienced a long duration of therapy. Intolerance in these patients might also be attributed to receiving dose-escalated dosing.

Monitoring the Response to Imatinib Therapy

Although imatinib has clearly demonstrated success as front-line therapy for CML, approximately 30% of patients discontinue imatinib therapy because of intolerance or primary or acquired resistance.⁵⁷ In the treatment of CML, failure to meet defined goals for hematologic, cytogenetic, and molecular assessments at specific time points constitutes primary resistance to imatinib, whereas losing response after having achieved these goals is defined as secondary resistance. Initial estimates of primary resistance were 15-24% at 18 months of follow-up and those of secondary resistance were 7-15%.⁵⁸ However, in recent estimations, approximately 40% of patients are at a risk of losing the complete cytogenetic response achieved.⁵⁸

Treatment goals, in chronologic order and order of importance, are complete hematologic response, complete cytogenetic response, major

molecular response, and complete molecular response. Hematologic responses are evaluated based on blood counts and differentials, and cytogenetic response assessments are based on the examination of Ph+ marrow cell metaphases, whereas molecular responses are based on quantitative assessments of the level of *BCR-ABL* transcripts. The definitions of responses achieved with CML therapy are outlined in Table 5.³⁹

In order to guide treatment decisions, time to response with imatinib therapy is often used to assess whether the responses to imatinib 400 mg/day are optimal or constitute failure or suboptimal responses in previously untreated patients with chronic-phase CML. Goals of imatinib therapy are that patients should achieve at least complete hematologic response at 3 months, minor cytogenetic response at 6 months, major cytogenetic response at 12 months, and complete cytogenetic response at 18 months. Criteria for failure or suboptimal response for patients receiving imatinib are listed in Table 6.³⁹ Failure implies that other treatment strategies should be considered, whereas suboptimal responses imply that although the patient might still derive some benefit from imatinib therapy, long-term outcome with therapy might not be optimal.³⁷

Monitoring is an important tool in obtaining the best possible outcomes for patients with CML.⁵⁷ The goal of monitoring responses to tyrosine kinase inhibitor therapy is to identify those patients who have achieved a “safe haven” response, which is defined as a stable confirmed major molecular response, and those who may have a better long-term outcome if they switched to a second-line therapy—either another tyrosine kinase inhibitor or autologous stem cell transplantation. In some patients, an escalated dose of imatinib or better compliance may improve response.⁵⁷

Table 5. Definitions of Responses in Chronic Myeloid Leukemia

Response	Definition
Complete hematologic response	Normal CBC Platelet count < 450 x 10 ³ /mm ³ WBC < 10 x 10 ³ /mm ³ Differential: < 5% basophils; no myelocytes, promyelocytes, or myeloblasts Nonpalpable spleen
Cytogenetic responses	
Minimal	66–95% Ph+ metaphases
Minor	36–65% Ph+ metaphases
Partial	1–35% Ph+ metaphases
Complete	0% Ph+ metaphases
Molecular responses	
Major	Ratio of <i>BCR-ABL</i> : <i>ABL</i> ≤ 0.1% on the international scale
Complete	Undetectable levels of <i>BCR-ABL</i> mRNA by RT-PCR

CBC = complete blood cell count; WBC = white blood cell count; Ph+ = Philadelphia chromosome–positive; mRNA = messenger RNA; RT-PCR = real-time polymerase chain reaction.
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The basis of tyrosine kinase inhibitor response monitoring is bone marrow cytogenetic analysis during the first 12–18 months by chromosome banding analysis of marrow metaphases, regular assessment of the *BCR-ABL* transcript levels by real-time quantitative PCR (RT-PCR) assay and selective testing for *BCR-ABL* kinase domain mutations. Although interphase fluorescence in situ hybridization and drug level assessment may also be necessary in some patients, chromosome banding analysis is the preferred method of cytogenetic testing.⁵⁷ Evidence from clinical trials indicates that the risk for loss of a major cytogenetic response or a complete hematologic response and subsequent transformation to accelerated phase or blast crisis occurs most often in the first 2–3 years of imatinib therapy.

Table 6. Definitions of Responses to Front-Line Imatinib Therapy

Time After Diagnosis	Response		
	Optimal	Suboptimal	Failure
3 mo	≥ CHR	No CyR	< CHR
6 mo	≥ minor CyR	< PCyR	No CyR
12 mo	≥ major CyR	< PCyR	< PCyR
18 mo	≥ CCyR	< MMR	< CCyR
Anytime during therapy	Stable or improving MMR	Loss of MMR, mutation	Loss of CHR or CCyR, mutation, CCA or Ph+

CHR = complete hematologic response; CyR = cytogenetic response; PCyR = partial cytogenetic response; CCyR = complete cytogenetic response; MMR = major molecular response; CCA = clonal chromosome abnormalities; Ph+ = Philadelphia chromosome–positive.
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Table 7. Monitoring Guidelines for Patients with Chronic Myeloid Leukemia

Assessment	Initial Monitoring	Subsequent Monitoring
Hematologic response	Every 15 days until complete hematologic response is achieved	Every 3 mo once complete hematologic response is achieved
Cytogenetic response	At 3 and 6 mo, then every 6 mo until complete cytogenetic response is confirmed	Every 12 mo only for occurrence of treatment failure or suboptimal response; unexplained anemia, leukopenia, and/or thrombocytopenia; and if regular molecular monitoring cannot be assured
Molecular response	Every 3 months until major molecular response is confirmed	At least every 6 mo
Mutation status	Immediately after detection of imatinib failure or suboptimal response, and before changing to second-line therapy	

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After this period, there is a sharp decline in risk for loss of response.⁵⁷

During initial diagnostic procedures, blood counts and differentials, bone marrow cytogenetics, and morphology are necessary to substantiate the diagnosis of chronic-phase CML and to determine the baseline presence of additional cytogenetic abnormalities. Once imatinib therapy is initiated, bone marrow studies should be done at 3, 6, and 12 months.³⁹ Guidelines for monitoring responses are outlined in Table 7.³⁹ Cytogenetics are required at 3 and 6 months, then every 6 months until complete cytogenetic response is confirmed. Ongoing marrow cytogenetic studies are not indicated unless those responses are lost or unexpected cytopenias occur, as the latter can be an indication of the emergence of myelodysplasia or acute myeloid leukemia, or more rarely, a Ph+ blast crisis. Although cytopenias are to be expected during the first 3–6 months in many cases, occurrences later during therapy may be an indication of marrow abnormalities, which should be evaluated. Hence, in cases of myelodysplastic features, suboptimal response, or imatinib failure, or if molecular monitoring cannot be assured, cytogenetic testing must be performed every 12 months. Molecular monitoring must be done every 3 months until major molecular response is confirmed, and at least every 6 months thereafter.^{39, 57}

Because the attainment of a major molecular response appears to represent stable disease control, until such a response is achieved and confirmed, RT-PCR for *BCR-ABL* transcript levels should be conducted using peripheral blood samples every 3 months during the first 12 months of therapy.⁵⁷ Once a major molecular response occurs, such monitoring can be reduced to every 6 months. The NCCN recommends that

if there is any 1-log increase in *BCR-ABL* transcripts, then analysis should be repeated in 1 month, and if the increase is confirmed, then monitoring should be done every month.³⁶ As monitoring of mutations is becoming increasingly important, mutation assays may be considered when there are elevations in *BCR-ABL* transcripts. There is consensus that mutation testing should be done when a switch to second-line therapy is contemplated, as this allows for more informed treatment choice.^{39, 57}

The Challenge of Relapse and Resistance to Imatinib Therapy

The development of resistance to therapy is a common dilemma in cancer treatment. Better understanding of molecular underpinnings of imatinib resistance has led to the rational development of therapeutic agents that target these resistance mechanisms, which are outlined below.⁵⁸

BCR-ABL–Dependent Mechanisms of Resistance

Several putative mechanisms of resistance to imatinib in patients with CML have been proposed, including structural modifications in *BCR-ABL*, overexpression or amplification of *BCR-ABL*, overproduction of other tyrosine kinases, and modulation of activity of drug influx transporters. Of these, the best-characterized mechanisms for resistance to imatinib are mutations in the *BCR-ABL* kinase domain. Point mutations in the *BCR-ABL* kinase domain have been described in 30–50% of patients with imatinib-resistant disease, although this may occur in 60–90% of patients with acquired imatinib resistance.^{59, 60} Although many

mutations do not affect the binding of the drug, clinically relevant mutations can prevent imatinib binding by disrupting drug contact points or promoting the active conformation of BCR-ABL to which imatinib cannot bind.^{60–62} The T315I mutation affects a contact residue that is necessary for imatinib binding to Abl kinase, in addition to creating steric hindrance to the binding of imatinib, which confers resistance to tyrosine kinase inhibitors in general.⁶³ Several additional mutations have been described in various structural domains of the *BCR-ABL* gene including the P-loop, C-helix, SH2 domain, substrate binding site, A-loop, and C-terminal lobe, with varying levels of impact on imatinib resistance. BCR-ABL mutations with high levels of resistance to imatinib include Y253H, F255K, and parental Ba/F3. However, with the exception of the T315I mutation, newer and more potent tyrosine kinase inhibitors demonstrate activity against most BCR-ABL mutations.^{58, 60, 62}

BCR-ABL–Independent Mechanisms of Resistance

Additional mechanisms of resistance to imatinib that do not involve BCR-ABL have been described. Alterations in drug efflux mechanisms might play a role in some cases of imatinib failure. Increased expression of the P-glycoprotein (P-gp) efflux pump has been demonstrated in resistant cell lines, and downregulation or inhibition of this pump has restored imatinib susceptibility to previously resistant cell lines.⁵⁸ However, the clinical relevance of these findings has yet to be established.⁵⁸ In addition, polymorphisms of the multidrug resistance gene have been identified in some instances of imatinib resistance that might be associated with differential rates of major molecular response.⁶⁴

Recently, uptake transporters, particularly the organic cation transporter hOCT1, have been implicated in imatinib resistance. Inhibition of hOCT1 was correlated with a decrease in receptor-mediated uptake of imatinib in *in vitro* studies.^{65, 66} Of interest, reduced levels of hOCT1 in the bone marrow mononuclear cells in patients who failed to achieve at least a major cytogenetic response have been noted as well.⁶⁷ The Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) trial found that patients with lower levels of hOCT1 had reduced rates of major molecular response at 12 months during standard-dose imatinib therapy compared with the rate of major molecular response achieved with high-dose

imatinib.⁶⁸ The effect of this on rates of imatinib resistance and overall survival has yet to be determined.⁵⁸

Preclinical evidence indicates that sequestration of imatinib in the plasma by the serum protein α_1 -acid glycoprotein might represent another possible imatinib resistance mechanism,^{69, 70} which needs to be corroborated in clinical studies.⁵⁸ A possible correlation between imatinib trough concentrations and rates of cytogenetic and molecular responses has also been proposed, but robust data are lacking to support this contention.^{58, 71, 72} Activation of alternative signaling pathways mediated by the Src family of kinases (SFK), among others, might also play a role in resistance.^{58, 73–75} Finally, epigenetic modifications have been implicated in the development of imatinib resistance. Upregulation of classes I and III deacetylases (HDAC) and downregulation of histone acetyltransferases were observed in an imatinib-resistant CML cell line.⁷⁶ To our knowledge, HDAC inhibitors have not been developed as clinical therapies for patients with imatinib-resistant disease.⁵⁸

Overcoming Resistance

Therapeutic strategies employed to achieve the best possible outcomes in patients who fail initial therapy, relapse, or who demonstrate a suboptimal response include imatinib dose escalation, switch to second-generation tyrosine kinase inhibitors, and autologous stem cell transplantation. The choice is determined by several factors, including patient age, presence of *ABL* mutations, and evidence of patient compliance or noncompliance with therapy.

Dose Escalation

It was hypothesized that resistance to standard-dose imatinib due to overexpression of Bcr-Abl protein, amplification, and/or mutations in *BCR-ABL* gene could be overcome with higher concentrations of imatinib.^{59, 77} Dose escalation of imatinib was initially evaluated in patients who showed suboptimal response or resistance to initial therapy at the standard dose. Fifty-four patients with Ph+ chronic-phase CML in hematologic or cytogenetic resistance or relapse to standard imatinib therapy were treated with higher doses of 800 mg/day (47 patients) or 600 mg/day (7 patients).⁷⁸ Of 20 patients treated for hematologic resistance or relapse, 13 (65%) achieved a complete or partial hematologic response, whereas 19 (56%) of 34 patients treated

for cytogenetic resistance or relapse achieved a cytogenetic response. In IRIS, patients initially treated with imatinib 400 mg/day who did not meet certain response criteria or who relapsed while taking therapy received higher doses of imatinib—first 600 mg/day and then 800 mg/day.⁷⁹ The stepwise escalation was used to minimize adverse events because the tolerability of imatinib was not well known when the study was initiated. Of the 553 patients enrolled in IRIS, 106 who met the criteria for dose escalation had their daily dose increased to 600 mg. Of those patients, 59 ultimately had a second increase to 800 mg/day. The rates of freedom from progression (to accelerated phase or blast crisis) and overall survival were 89% and 84%, respectively, 3 years after the dose increase.⁷⁹ Sixty-seven percent of patients who received dose escalations based on the ELN recommendations³⁷ attained or recovered a hematologic response within 12 months of the escalation, and 38% attained or regained a cytogenetic response.

In another study of 84 patients with chronic-phase CML, including patients who had experienced cytogenetic or hematologic failure to imatinib, imatinib dose escalation from 400 to 800 mg/day (72 patients) or from 300 to 600 mg/day (12 patients) resulted in a complete cytogenetic response rate of 40%.⁸⁰ Overall survival was 69% at a median follow-up of 61 months after dose escalation; event-free survival at 3 years was 47%. The higher doses of imatinib were well tolerated, and 76% of patients continued to receive 100% of the intended dose at 12 months. In contrast to previous implications that responses to dose escalation might be transient, these results suggested that dose escalation produced durable responses in a subset of patients with cytogenetic failure to previous imatinib therapy.^{81, 82} These and other results also showed that dose escalation in the setting of resistance should be only reserved for patients who failed standard-dose imatinib. Moreover, dose escalation is unlikely to benefit patients who never achieved a cytogenetic response to standard-dose imatinib or those with hematologic failure. However, results of dose-escalation studies in patients who experienced imatinib failure have to be considered in the context of results with other available therapies, including second-generation tyrosine kinase inhibitors and stem cell transplantation, which will be discussed in subsequent sections.

Recently, a prospective, international, multicenter, phase III trial that randomized 227 patients with

pretreated late Ph+ chronic-phase CML to either standard-dose imatinib 400 mg/day, or high-dose imatinib 800 mg/day for 6 months followed by 400 mg/day as a maintenance dose, demonstrated significantly higher rates of both major cytogenetic response (21% vs 37%, $p=0.01$) and complete cytogenetic response at 3 months (6% vs 25%, $p<0.001$) with high-dose imatinib.⁸³ The majority of patients had previously received hydroxyurea; other pretreatments included IFN, busulfan, and cytarabine. Although major cytogenetic response (34% vs 54%, $p=0.009$) and complete cytogenetic response (20% vs 44%, $p<0.001$) were still significantly higher with high-dose imatinib therapy compared with the standard dose at 6 months, this benefit was not sustained. At 12 months, the rates of major cytogenetic response (57% for high-dose vs 59% for standard-dose imatinib) were comparable between the two treatment arms. Moreover, the occurrence of grades 3 and 4 hematologic toxicities was higher for patients receiving high-dose therapy compared with those who received standard-dose imatinib. After 6 months, patients in the high-dose arm experienced a loss of major cytogenetic response (53.5% vs 72.4%, $p=0.14$) and complete cytogenetic response (54.3% vs 82.4%, $p=0.07$) less frequently than those in the standard-dose arm. However, as pretreated patients with late-phase CML represented only a small subset of the total CML patient population in this study, the clinical applicability of these results is limited.

The imatinib dose of 400 mg/day used in IRIS was based on early trials demonstrating good tolerability and hematologic response in patients with chronic-phase CML. However, the optimal front-line dose required to achieve durable cytogenetic and molecular responses and produce prolonged progression-free survival has not been established. Therefore, several studies, including the TOPS study and the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) 021/ELN high-dose imatinib trial, are being conducted to evaluate the front-line use of higher doses of imatinib to overcome primary resistance.^{84, 85} The phase III TOPS trial compared the efficacy and safety of high-dose imatinib 800 mg/day with standard-dose imatinib 400 mg/day in patients with newly diagnosed chronic-phase CML.⁸⁴ The study's primary end point was the major molecular response rate at 12 months of therapy. The 24-month data showed no significant difference between the two groups (high dose vs standard dose) for either the complete cytogenetic response rate (76% vs 76%, $p=0.100$) or the major

molecular response rate (51% vs 54%, $p=0.626$). Event-free survival was 95% for both arms ($p=0.71$), and progression-free survival was 98% and 97% for the two arms, respectively ($p=0.70$). Furthermore, adverse events occurred more often among patients in the high-dose imatinib group compared with the standard-dose group, and the rate of discontinuation due to adverse effects was higher as well (12% vs 5%).⁸⁵

In the second 021/ELN study, 216 patients with high-risk Sokal scores were randomized to imatinib 800 mg/day or 400 mg/day as front-line therapy.⁸⁶ The results of this trial were similar to those of the TOPS trial and showed no statistically significant differences between the two arms for the primary end point of complete cytogenetic response at 12 months; 64% and 58% of patients in the 800-mg/day and the 400-mg/day groups achieved complete cytogenetic responses. Although there was a trend toward higher rates of major molecular response in the 800-mg/day group, this was not statistically significant. The frequency of adverse events was similar in both groups, but compliance was poorer in the 800-mg group, with 62% taking more than 600 mg/day compared with 87% in the 400-mg/day group taking more than 350 mg/day. The dose-escalation trials in the front-line setting showed that use of higher doses of imatinib were not associated with benefit in terms of complete cytogenetic response or major molecular response, which might be attributable to dose interruptions and compliance issues.

Second-Generation Tyrosine Kinase Inhibitors

Dasatinib and nilotinib are second-generation tyrosine kinase inhibitors that were rationally designed to improve binding affinity against Bcr-Abl and improve specificity over that of imatinib. Both these agents have demonstrated greater potency than imatinib and shown preclinical efficacy against a broad range of BCR-ABL kinase domain mutations, with the exception of T315I.^{60, 87} Dasatinib is approximately 325-fold more potent than imatinib and 16-fold more potent than nilotinib against wild-type BCR-ABL. Nilotinib is approximately 30 times more potent in vitro than imatinib against wild-type BCR-ABL.⁶⁰

Similar to imatinib, nilotinib also binds to the inactive/closed conformation of the Bcr-Abl tyrosine kinase that inhibits the kinase activity of Bcr-Abl but exhibits a higher affinity for the kinase. Current evidence indicates that cellular import of nilotinib might not be mediated by

hOCT1, with some clinical implications in terms of developing resistance.⁸⁸ The structural similarities of both imatinib and nilotinib result in a similar profile of protein kinase targets. However, dasatinib has a very different structure and binds to both the inactive/closed and active/open conformation of BCR-ABL and SFK, with putative activity against several imatinib-resistant ABL mutations as well as a number of additional tyrosine kinase families potentially involved in mediating imatinib resistance. By the same token, dasatinib also has more off-target kinase targets compared with imatinib and nilotinib.⁵⁸ Table 8 shows the pharmacokinetic parameters of imatinib, dasatinib, and nilotinib.⁸⁹

All three tyrosine kinase inhibitors are available orally. The maximum plasma concentration of all three tyrosine kinase inhibitors is achieved within 0.5–6 hours.⁸⁹ Whereas imatinib absorption is not influenced by food or antacid use,⁹⁰ a 14% increase in the area under the curve (AUC) may occur in patients taking dasatinib with a high-fat meal,³ and an 82% increase in systemic exposure occurs when nilotinib is taken with a high-fat meal compared with the fasted state.⁹¹ Moreover, decreased availability of dasatinib was noted when taken in combination with antacids.⁹² Concomitant use of dasatinib with histamine₂-blockers decreased dasatinib exposure by up to 61%, whereas its exposure was reduced 2-fold when used in combination with proton pump inhibitors.^{48, 89, 92}

Imatinib is primarily metabolized via the cytochrome P450 (CYP) enzymes CYP3A4 and CYP3A5; other enzymes play a minor role (CYP2D6, CYP2C9, CYP2C19, and CYP1A2). Dasatinib is extensively and primarily metabolized by CYP3A4, as is nilotinib. It appears that nilotinib is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6, and UGT1A1. Nilotinib may induce CYP2B6, CYP2C8, and CYP2C9.^{89, 93} As the CYP3A4 pathway is a common metabolic pathway for many drugs, interactions can be expected with the tyrosine kinase inhibitors sharing this pathway. Drug-drug interactions for all three tyrosine kinase inhibitors are presented in Table 9.⁸⁹

Trial Evidence for Dasatinib in Chronic Myeloid Leukemia

Early clinical trials of dasatinib in patients with chronic-phase CML who had failed imatinib therapy provided compelling evidence of the antileukemic activity of this second-generation

Table 8. Pharmacokinetic Parameters of Tyrosine Kinase Inhibitors for the Treatment of Chronic Myeloid Leukemia

Drug	Absolute Bioavailability (%)	Protein Binding (%)	T _{max} (hrs)	Half-Life (hrs)	AUC ₀₋₂₄ (µg•hr/ml)	Volume of Distribution (L)	C _{trough} (ng/ml)
Imatinib	98	~95	2-4	18	40.1	295	1215.8
Dasatinib	Unknown	~96	0.5-6	3-5	Unknown	2505	Unknown
Nilotinib	Unknown	~98	3	17	36.0	579	900.2

T_{max} = time to maximum concentration; AUC₀₋₂₄ = area under the concentration-time curve from 0-24 hrs; C_{trough} = trough concentration.

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Table 9. Drug-Drug Interactions for the Tyrosine Kinase Inhibitors Used to Treat Chronic Myeloid Leukemia

Drug	Interacting Drug			
	Inducer	Effect	Inhibitor	Effect
Imatinib	Phenytoin	Decreased imatinib AUC	Ketoconazole	Decreased clearance (28.6%), increased C _{max} (26%), and AUC _{24-∞} (40%, 40%)
	Rifampin	Decreased imatinib C _{max} (54%) and AUC _{24-∞} (68%, 74%)	Cyclosporine Elacridar	Increased exposure of imatinib Increased brain penetration and systemic exposure
	St. John's wort	Increased oral clearance (44%) of imatinib		
	Antiepileptic drugs (carbamazepine, oxcarbazepine, phenytoin, phenobarbital, primidone)	Decreased C _{max} , AUC, T _{max} , and half-life; increased oral clearance	Pantoprazole	Increased systemic exposure of imatinib
Dasatinib	Rifampin	Decreased dasatinib AUC (82%)	Valspodar	Increased brain penetration
	Famotidine	Decreased dasatinib exposure (61%)	Zosuquidar	Increased brain penetration
Nilotinib	Rifampin	Decreased nilotinib AUC (80%)	Ketoconazole	Increased nilotinib AUC (3-fold)

AUC = area under the concentration-time curve; C_{max} = maximum concentration; AUC_{24-∞} = AUC from 24 hrs extrapolated to infinity; T_{max} = time to maximum concentration.

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tyrosine kinase inhibitor. Dasatinib was approved based on the results of four single-arm multicenter studies in patients with CML who were resistant to or intolerant to imatinib.³ The primary efficacy end point was a major cytogenetic response in patients with chronic-phase CML and a major hematologic response in patients with accelerated-phase, myeloid-phase, and lymphoid blast-phase CML, and Ph+ acute lymphoblastic leukemia. A total of 445 patients were enrolled in the four studies. Among patients with chronic-phase CML, 45% achieved a major cytogenetic response, and 33% achieved a complete cytogenetic response. A major hematologic response was achieved in 59% of patients with accelerated-phase CML, 32% with myeloid CML, 31% with lymphoid-blast CML, and 42% with Ph+ acute lymphoblastic leukemia. Common adverse effects of the drug included myelosuppression, bleeding, and fluid retention. Pleural effusion of any grade occurred in 22% of

patients, and the rate of grade 3 or 4 pleural effusion was 5%.

In the phase II, international SRC/ABL Tyrosine Kinase Inhibition Activity Research Trials of Dasatinib (START)-C trial, dasatinib 70 mg twice/day was evaluated in 387 patients with chronic-phase CML who were resistant (288 patients) or intolerant (99 patients) to imatinib.⁹⁴ In this initial report of 186 patients with imatinib-resistant or -intolerant chronic-phase CML, 90% of patients achieved a complete hematologic response, and 52% achieved a major cytogenetic response. These responses were durable, with only 2% of patients who achieved a major cytogenetic response progressing or dying of their disease. At 9 months, dasatinib demonstrated the ability to induce molecular responses, reducing BCR-ABL:ABL transcript ratios from 66% at baseline to 2.6%. In the 24-month follow-up, a 2-year major cytogenetic response rate of 62% and a complete cytogenetic response

Table 10. Efficacy of Dasatinib and Nilotinib as Second-Line Therapy in Patients with Chronic Myeloid Leukemia^{49, 95-97}

Efficacy Measure	Dasatinib		Nilotinib	
	Chronic Phase (n=387)	Accelerated Phase (n=159)	Chronic Phase (n=321)	Accelerated Phase (n=137)
Complete hematologic response	91%	52%	94%	31%
Major cytogenetic response	62%	43%	59%	32%
Complete cytogenetic response	53%	33%	44%	20%
Progression-free survival	80%	55%	64%	NR
Overall survival	94%	72%	87%	67%

Data are percentages of patients.

rate of 53% were achieved.⁹⁵ The estimated 2-year progression-free survival was 80% and the 2-year overall survival rate was 94% (Table 10).⁹⁵ Grade 3 or 4 thrombocytopenia and neutropenia were noted in 49% and 50%, respectively, of patients. Pleural effusions occurred in 26% of patients overall, with 9% experiencing severe adverse events. Based on these trials, the initial recommended dosage of dasatinib was 70 mg twice/day for all indications.

Subsequently, the label of dasatinib was modified to initiate therapy with 100 mg once/day for patients with chronic-phase CML. This was based on results of a phase III study conducted in 670 patients with chronic-phase CML who had resistance, intolerance, or suboptimal response to imatinib.⁴⁶ The study evaluated dasatinib 100 mg once/day compared with 50 mg twice/day, 140 mg once/day, or 70 mg twice/day. At the 2-year follow-up, dasatinib 100 mg once/day was as efficacious as the other dosage groups in terms of major cytogenetic response and complete cytogenetic response rates. Progression-free survival and overall survival rates were 80% and 91%, respectively, for 100 mg once/day. Cytogenetic responses occurred quickly and predicted ultimate clinical outcome to a degree. Among patients treated with dasatinib 100 mg once/day, only 50% of patients who achieved a partial cytogenetic response by 6 months were likely to achieve complete cytogenetic response by 2 years, whereas the likelihood of achieving a complete cytogenetic response by 2 years dropped to 8% or less in patients who achieved a minor, minimal, or no cytogenetic response at 6 months. However, disease transformation to accelerated phase or blast crisis occurred in only 3% of patients in the trial.

Limited therapeutic options exist for patients with accelerated-phase disease. A phase III study evaluated the efficacy and safety of two dosing

regimens of dasatinib, 140 mg once/day and 70 mg twice/day, in 317 patients with accelerated-phase CML who were resistant or intolerant to imatinib (Table 10).⁹⁶ At a median follow-up of 15 months, the rates of major hematologic response (66% vs 68%) and major cytogenetic response (39% vs 43%) were comparable for the 140-mg once/day versus the 70-mg twice/day cohorts. The estimated progression-free survival rates were 51% and 55% for the once/day and twice/day groups, respectively, at 24 months, and overall survival rates were 63% and 72%, respectively. However, the once/day regimen had an improved safety profile. A significantly lower proportion of patients experienced pleural effusion ([all grades] 20% vs 39%, $p < 0.001$) in the once/day group.

A meta-analysis of three phase II-III dasatinib trials in patients with chronic-phase CML evaluated response in the context of preexisting BCR-ABL mutations.⁹⁸ Among 1043 patients in these trials, 39% had preexisting BCR-ABL mutations, and 63 different mutations were found. At the 2-year follow-up, imatinib-resistant patients with and without mutations showed differences in response rates. Forty-three percent of patients with mutations achieved a complete cytogenetic response and 70% had a durable progression-free survival compared with 47% and 80%, respectively, in patients without mutations. Nonetheless, high response rates were achieved with many different mutations, with the notable exception of T315I.

As noted, adverse events associated with dasatinib therapy are mostly mild to moderate. However, pleural effusion is a complication of dasatinib therapy, occurring in approximately 35% of patients, in whom 17% are grade 3 or 4. The occurrence of pleural effusion is more common in patients with accelerated-phase or blast crisis CML.⁴⁶⁻⁴⁸ Other factors associated

Table 11. Phase II Studies of Dasatinib and Nilotinib as Front-Line Therapy in Patients with Chronic-Phase Chronic Myeloid Leukemia¹⁰¹⁻¹⁰³

Response	No. (%) of Patients		
	Dasatinib	Nilotinib	Nilotinib
Best			
Complete hematologic response	65 (95)	55 (100)	NR
Complete cytogenetic response	70 (96)	58 (98)	NR
Major molecular response	70 (79)	60 (88)	NR
Complete molecular response	70 (11)	60 (22)	NR
At 12 months			
Complete cytogenetic response	49 (94)	42 (95)	73 (96)
Major molecular response	50 (74)	41 (81)	73 (85)

NR = not reported.

with development of pleural effusion include a history of cardiac disease, hypertension, and a twice/day dasatinib regimen.⁹⁹ It has been proposed that the underlying cause might be off-target kinase inhibition, and the relatively lower incidence during imatinib therapy might relate to the stronger PDGFR β inhibition mediated by dasatinib. Management of pleural effusion included temporary cessation of dasatinib therapy in 83% of patients, diuretics in 71%, pulse steroids in 27%, and thoracentesis in 19%.⁹⁹ Platelet dysfunction is also more likely to occur with dasatinib therapy than with imatinib.¹⁰⁰

Recently, a phase II trial evaluated the efficacy and safety of front-line dasatinib in 62 patients with previously untreated CML in early chronic phase who were randomized to receive either dasatinib 50 mg twice/day or dasatinib 100 mg once/day (Table 11).¹⁰¹ The primary objective of this study was to estimate the proportion of patients achieving major molecular response at 12 months. Of the 65 patients who were not in complete hematologic response at the start of treatment, 95% of patients achieved complete hematologic response. Ninety-six percent of 70 patients who had at least 3 months of follow-up achieved complete cytogenetic response, whereas 79% (55/70) of patients with CML in early chronic phase achieved major molecular response. Grade 3 or 4 nonhematologic adverse events included muscle or joint pain (14%), fatigue (11%), dyspnea (8%), and neuropathy (7%); grade 3 or 4 hematologic toxicity included neutropenia (25%), thrombocytopenia (24%), and anemia (10%). Pleural effusion occurred in 17% of evaluable patients, with grade 3 or 4 pleural effusion observed in 3% of patients. The dasatinib 100-mg/day arm continues to accrue patients due to improved response and toxicity.

Trial Evidence for Nilotinib in Chronic Myeloid Leukemia

Nilotinib showed in vitro activity against imatinib-resistant CML cell lines in preclinical studies.¹⁰⁴ An early phase I, dose-escalation study found that of 33 patients with blast crisis CML, 13 patients achieved a hematologic response and 9 patients achieved a cytogenetic response.¹⁰⁵ Of the 46 patients with accelerated-phase CML, 33 patients achieved a hematologic response whereas 22 patients achieved a cytogenetic response; 11 of 12 patients with chronic-phase CML achieved a complete hematologic response. Common adverse events were myelosuppression, transient indirect hyperbilirubinemia, and rashes.

A phase II, open-label study found that nilotinib 400 mg twice/day induced a major cytogenetic response in 48% of 280 patients with chronic-phase CML resistant or intolerant to imatinib.¹⁰⁶ Complete cytogenetic response occurred in 31% of patients, and partial cytogenetic response in 16%. The 12-month estimated survival was 95%. Nilotinib was well tolerated, and most adverse events were mild to moderate. Twenty-nine percent of patients had grades 3 or 4 neutropenia and thrombocytopenia, and 1% had pleural or pericardial effusions.

The U.S. Food and Drug Administration (FDA) approval of nilotinib for the treatment of chronic-phase and accelerated-phase Ph+ CML in adults who are resistant to or intolerant to imatinib was based on two single-arm, open-label phase II studies in patients with chronic-phase CML and accelerated-phase CML.^{49,97} In the chronic-phase CML trial of 321 patients who were imatinib resistant or intolerant, major cytogenetic response was achieved in 59% of patients, and complete cytogenetic response was achieved by

44% of patients with at least 2 years follow-up (Table 10).⁴⁹ Of the 114 patients who had a baseline complete hematologic response, 73% achieved major cytogenetic response whereas 58% achieved complete cytogenetic response. Estimated 2-year overall survival was 87% whereas median progression-free survival was 33.6 months. Treatment discontinuation was reported in 59% of patients, primarily due to disease progression (27%) or drug-related adverse events (15%). Grade 3 or 4 nonhematologic adverse events included rash, headache, and diarrhea occurring in 2% of patients, whereas grade 3 or 4 hematologic adverse events included neutropenia (31%), thrombocytopenia (31%), and anemia (10%). Pleural or pericardial effusions (all grades) occurred in 2% of patients, of which grade 3 or 4 pleural or pericardial effusions occurred in less than 1%.

In the accelerated-phase CML trial of 137 patients, complete hematologic response was achieved in 31% of patients after initiation of therapy, and major cytogenetic response was achieved in 32% of patients (Table 10).⁹⁷ Complete cytogenetic response was achieved in 20% of patients, with more than 70% of these patients remaining in complete cytogenetic response at 24 months. Estimated overall survival was 67% at 24 months.

In a phase II study, 73 previously untreated patients with early chronic-phase CML received nilotinib 400 mg twice/day.⁵¹ The primary end point was complete cytogenetic response at 1 year. At a median follow-up of 15 months, 96% of patients reached the primary end point, and the major molecular response rate was 85%.⁵¹ Response to nilotinib was rapid, with 78% of patients achieving a complete cytogenetic response and 52% of patients achieving a major molecular response by 3 months. During the first year's treatment, 52% of patients had treatment interruptions, mainly as the result of nonhematologic and biochemical adverse effects. One patient progressed to blast crisis after 6 months. An update of this trial, including a detailed analysis of the safety profile of nilotinib 400 mg twice/day, was recently reported.¹⁰³ The majority of patients (74%) received a mean daily dose of nilotinib 600–800 mg, whereas 18% and 8% of patients received 400–599 mg/day and less than 400 mg/day, respectively. Results demonstrated that 96% of patients achieved complete cytogenetic response at 12 months, and 85% of patients achieved major molecular response at 12 months with nilotinib therapy (Table 11). At 12

months, the complete cytogenetic response rate was similar for all mean daily doses of nilotinib. Grade 3 or 4 hematologic adverse events included neutropenia (4% of patients) and thrombocytopenia (3%). Four adverse events (grade 2 or higher) accounted for the majority of dose interruptions: bilirubin level increase (38%; no grade 4); skin rash and/or pruritus (37%; no grade 4); asymptomatic amylase and/or lipase level increase (16%; 4% grade 4); transaminase level increases (19%, no grade 4). Data from this trial further demonstrated the feasibility and safety, as well as the efficacy, of nilotinib 400 mg/day as front-line therapy in patients with previously untreated Ph+ CML in early chronic phase.

Another recent phase II trial also evaluated nilotinib as front-line treatment for patients with CML in early chronic phase. This single-arm study compared results from nilotinib 400 mg twice/day in 61 patients with newly diagnosed, Ph+ chronic-phase CML with historical control cohorts treated with imatinib 400 or 800 mg/day.⁵⁰ After 3 months of therapy with nilotinib, 81% of patients achieved a complete cytogenetic response, which further improved to 95% at 12 months. This compared very favorably to imatinib, which has historically produced a complete cytogenetic response in 40–60% of patients at 3 months and 60–90% at 12 months, depending on the dose. Moreover, 91% of patients in the nilotinib group maintained a complete cytogenetic response at 30 months, which was better than either imatinib control group. The majority of patients (81%) treated with nilotinib also achieved a major molecular response at 12 months. These data demonstrated that nilotinib was highly active in patients with newly diagnosed Ph+ chronic-phase CML and induced rapid responses with a favorable tolerability profile.

Compelling data from phase II studies led investigators to evaluate the benefits of nilotinib compared with the standard, imatinib, for initial treatment of CML. Results from the Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients (ENESTnd) trial, an international, randomized, phase III trial designed to compare nilotinib 300 or 400 mg twice/day with imatinib 400 mg/day, were recently reported.¹⁰⁷ A total of 846 patients with Ph+ chronic-phase CML who had been diagnosed within 6 months were randomized 1:1:1 to nilotinib 300 mg twice/day, nilotinib 400 mg twice/day, or imatinib 400 mg/day (Table 12). Randomization was stratified by Sokal risk score, and all patients had a minimum of 12 months of

Table 12. Efficacy of Nilotinib vs Imatinib in Newly Diagnosed Patients with Chronic-Phase Chronic Myeloid Leukemia in the ENESTnd Trial¹⁰⁷

Efficacy Measure	Nilotinib 300 mg b.i.d. (n=282)	Nilotinib 400 mg b.i.d. (n=281)	Imatinib 400 mg q.d. (n=283)
Major molecular response at 12 mo	44% (p<0.0001 ^a)	43% (p<0.0001 ^a)	22%
Median time to major molecular response	5.7 mo	5.8 mo	8.3 mo
Complete cytogenetic response at 12 mo	80% (p<0.0001 ^a)	78% (p=0.0005 ^a)	65%
Progression to accelerated phase or blast crisis	< 1% (p=0.0095 ^a)	1% (p=0.0037 ^a)	4%

ENESTnd = Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients.

^aFor the comparison with the imatinib group.

treatment or discontinued early. Treatment arms were balanced for age, median time since diagnosis, Sokal risk score, and previous therapy. Nilotinib demonstrated significantly higher rates of major molecular response at 12 months compared with imatinib (nilotinib 300 mg twice/day vs imatinib 400 mg/day: 44% vs 22%, p<0.0001; nilotinib 400 mg twice/day vs imatinib 400 mg/day: 43% vs 22%; p<0.0001). Median time to major molecular response was shorter for patients who received nilotinib compared with those who received imatinib (nilotinib 300 mg twice/day vs imatinib 400 mg/day: 5.7 vs 8.3 mo; nilotinib 400 mg twice/day vs imatinib 400 mg/day: 5.8 vs 8.3 mo). Moreover, 24% and 21% of patients who received nilotinib 300 mg twice/day and 400 mg twice/day, respectively, achieved a complete molecular response at any time as assessed by a 4-log reduction or a ratio of 0.0032% (International Scale) in *BCR-ABL* transcript levels compared with 10% of patients who received imatinib 400 mg/day. Nilotinib therapy also resulted in significantly higher rates of complete cytogenetic response by 12 months compared with patients who received imatinib (nilotinib 300 mg twice/day vs imatinib 400 mg/day: 80% vs 65%, p<0.0001; nilotinib 400 mg twice/day vs imatinib 400 mg/day: 78% vs 65%, p=0.0005). Progression to advanced disease was lower in patient cohorts that received nilotinib therapy compared with imatinib therapy.

Both nilotinib and imatinib were generally well tolerated in the ENESTnd study, and rates of discontinuation due to adverse events or laboratory abnormalities were comparable across all treatment arms.¹⁰⁷ In addition, no patients in ENESTnd demonstrated a QTc interval (determined by Friderica's formula) greater than 500 msec, and there was no decrease from baseline in mean left ventricular ejection fraction during any of the treatments. In summary, both nilotinib 300 mg and 400 mg twice/day demonstrated significant

superiority to imatinib 400 mg/day based on improved rates of major molecular response and complete cytogenetic response. Fewer patients treated with nilotinib progressed to accelerated phase or blast crisis, and the efficacy of nilotinib was observed across all Sokal scores. Trial investigators concluded that nilotinib may replace imatinib as the standard of care in patients with newly diagnosed CML.

Mutations Associated with Second-Generation Tyrosine Kinase Inhibitors

Although the mutagenic potential of nilotinib or dasatinib is lower than that of imatinib, new mutations, such as T315A and V299L mutations, have been described with the second-generation tyrosine kinase inhibitors. Specific *BCR-ABL* kinase domain mutations that occur with nilotinib and dasatinib, in some cases, did not confer resistance to imatinib.¹⁰⁸ Mutations in the aromatic ring in the side chain of phenylalanine 317, or the F317L mutation of *BCR-ABL* kinase domain confers resistance to dasatinib, but not to imatinib or nilotinib.^{109, 110} Dasatinib appears to select for this mutation, as it constitutes 50% of all mutations detected after dasatinib failure, as opposed to only 12% of mutations after imatinib failure (Table 13).¹¹¹ Although both the T315I and F317L mutations are associated with resistance to tyrosine kinase inhibitor therapy, they did not affect overall survival, which was dependent primarily on the stage of disease. Patients in chronic phase harboring T315I or F317L mutations still showed an indolent clinical course.^{51, 111} Mutations associated with nilotinib resistance are T315, Y253, and E255 residues.^{78, 108} Of note, some evidence suggests that treatment with second-generation tyrosine kinase inhibitors after imatinib failure was not more likely to select for the T315I mutation, with this mutation found in only 4% of patients.¹⁰⁸

Table 13. Selected Mutations That Affect Response to Tyrosine Kinase Inhibitors⁵⁸

Resistance	Imatinib	Dasatinib	Nilotinib	Bosutinib
Highly resistant (> 10-fold increase in IC ₅₀)	T315I	T315I	T315I	T315I
	E255V		E255V	V299L
Resistant (4.01–10-fold increase in IC ₅₀)	G250E	G250E	G250E	G250E
	E255K	E255K	E255K	E255V
	F486S	L248V	F359V	E255K
		V299L		
Moderately resistant (2.01–4-fold increase in IC ₅₀)	L248V	Q252H	L248V	L248V
	Y253F	E255V	Q252H	F317L
	D276G	L384M	Y253F	F486S
	E279K	F486S	E279K	
	F317L		F317L	
	F359V		L384M	
	H396P		H396P	
	H396R		H396R	

IC₅₀ = drug concentration that inhibits 50% of Bcr-Abl kinase activity (wild-type = 1).

Knowledge of the mutation status of a patient might guide therapeutic decisions. Thus, if a patient has a preexisting P-loop mutation, he or she may be more susceptible to dasatinib, and those with 299 and 317 mutations may do better with nilotinib, although such mutations do not preclude responses to either dasatinib or nilotinib. An interesting study conducted in 169 patients with chronic-phase CML who were switched from imatinib to second-generation tyrosine kinase inhibitors found that mutations detected before the tyrosine kinase inhibitor switch correlated with hematologic and cytogenetic responses and overall survival.⁷⁸ Some clinical evidence suggests that a fraction of patients who experience imatinib resistance might never achieve a complete cytogenetic response with further treatment. Patients who receive a second-generation tyrosine kinase inhibitor and fail to experience a cytogenetic response by 6 months have only a 10% probability of achieving a major cytogenetic response at 1 year.¹¹² Moreover, those who do not achieve a major cytogenetic response at 12 months have a 20% risk of disease progression over the next year.¹¹²

Emerging Drug Strategies for Chronic Myeloid Leukemia

Combination Drug Strategies

Efforts such as combination strategies are under way to optimize front-line therapy with the intent of improving molecular responses and overall survival compared with those achieved with single-agent therapies. Based on previous clinical

experience with IFN- α , imatinib is being tested in combination with IFN- α and cytarabine.²⁶ The German CML Study Group compared imatinib 800 mg/day (338 patients) with standard-dose (400 mg/day) imatinib (326 patients) and with standard-dose imatinib plus IFN (351 patients) in 1015 newly diagnosed patients with CML to compare molecular response at 12 months and survival in each treatment arm.¹¹³ Cumulative complete cytogenetic response achieved at 12 months with imatinib 400 mg/day, imatinib 800 mg/day, and imatinib 400 mg/day plus IFN were 52.3%, 64.9% and 50.6%, respectively, whereas major molecular response rates were 30.2%, 54.3% and 34.6%, respectively. Imatinib 800 mg/day also resulted in more rapid achievement of major molecular response compared with the other treatment arms. However, these response rates have not translated into better progression-free survival or overall survival; further follow-up data are awaited.

Interim results of a phase III, randomized, multicenter trial comparing imatinib 400 mg/day (159 patients) with imatinib 600 mg/day (160 patients), imatinib 400 mg/day plus cytarabine 20 mg/m²/day on days 15–28 of 28-day cycles (158 patients), and imatinib 400 mg/day plus pegylated IFN-2 α 90 μ g/week (159 patients) were recently reported.¹¹⁴ The 18-month update of this two-part study confirmed earlier results of the superiority of imatinib 400 mg/day plus pegylated IFN-2 α compared with the control arm (imatinib 400 mg/day) in terms of major molecular response at 24 months (71% vs 48%, $p < 0.0001$) and undetectable minimal residual

disease at 24 months (22% vs 11%, $p=0.0028$). Similarly, optimal molecular response, defined as 4-log reduction in level of *BCR-ABL* transcripts was significantly higher with the imatinib 400 mg/day plus pegylated IFN-2 α combination therapy compared with standard imatinib therapy (46% vs 26%, $p=0.0006$). Grade 3 or 4 neutropenia was higher in the imatinib 400-mg/day plus pegylated IFN-2 α combination arm compared with the control arm (49% vs 7%), but this did not translate into higher rates of infection. Based on these results, accrual into the imatinib 600 mg/day and imatinib 400 mg/day plus cytarabine arms was stopped. The second part of the trial is ongoing to confirm whether achieving higher molecular responses will provide a survival advantage.

Investigational Agents

A number of novel agents are under investigation to further expand the armamentarium of treatment options for patients with CML. Bosutinib, an orally available dual Src-Abl inhibitor is 200 times more potent than imatinib. This agent has minimal activity against c-kit and PDGFR, which may explain its benign toxicity profile in terms of myelosuppression and fluid retention. In the phase I portion of a phase I–II study in patients with chronic-phase CML resistant to or intolerant to imatinib, bosutinib 600 mg/day resulted in dose-limiting skin toxicity.¹¹⁵ In the phase II component of the study in which 283 patients received bosutinib 500 mg/day, 79% of 67 imatinib-resistant evaluable patients achieved a complete hematologic response. Of 84 imatinib-resistant patients evaluable for cytogenetic response, 34 (40%) achieved a major cytogenetic response including 24 (29%) with a complete cytogenetic response. Twenty (33%) of 60 evaluable patients achieved major molecular response, half of which were complete molecular responses. Among imatinib-intolerant patients, 22 (76%) of 29 evaluable patients achieved complete hematologic response, and 13 (59%) of 22 evaluable patients achieved major cytogenetic response. Grade 3 or 4 adverse events included diarrhea (8%), rash (8%), and increased alanine aminotransferase level (5%); one patient with a pretreatment history of pleural effusions experienced pleural effusion accompanied by pneumonia.

AP24534 is an oral multikinase inhibitor that has been designed as a pan-*BCR-ABL* inhibitor. It inhibits both wild-type and T315I *BCR-ABL*

KD mutants in addition to Flt-3 and c-Src. In a phase I study of 32 patients with refractory CML and other hematologic malignancies, 27 patients had a diagnosis of CML, mostly in the chronic phase and 12 patients harbored T315I mutation.¹¹⁶ All of the patients with CML had received previous imatinib, whereas 94% and 54% of patients had received previous dasatinib and nilotinib, respectively; 83% had resistance to three or more tyrosine kinase inhibitors. No dose-limiting toxicities were observed at doses up to 30 mg. Grade 3 or 4 adverse events included thrombocytopenia and neutropenia, and QTc-interval prolongation was reported in one patient. Sixteen (89%) of 18 patients with chronic-phase CML achieved a complete hematologic response, whereas two of four patients with accelerated-phase CML achieved a major hematologic response. Of 12 patients with a T315I mutation, seven achieved a complete hematologic response with AP24534. A phase II study to explore use of this agent in patients with imatinib-resistant, dasatinib-resistant, and nilotinib-resistant disease, as well as those with a T315I mutation, is being planned.

Given that the T315I mutation has posed a considerable challenge for the currently available, small-molecule, ATP-competitive tyrosine kinase inhibitors, alternative strategies are being sought. Omacetaxine mepesuccinate is a semisynthetic form of homoharringtonine, a putative protein synthesis inhibitor that has a mechanism of action that is independent of tyrosine kinase inhibition. A multicenter, single-arm phase II–III study enrolled 81 patients with CML for whom imatinib treatment had failed and who had a T315I mutation at baseline, 49 in chronic phase, 17 in accelerated phase, and 15 in blast crisis.¹¹⁷ The drug was given subcutaneously, with an induction phase that involved twice-daily administration for 14 days of a 28-day cycle. After a complete hematologic response was achieved, patients received a maintenance regimen with twice-daily administration for 7 days of a 28-day cycle. At a median follow-up of 6.4 months, complete hematologic response occurred in 86% of patients with chronic-phase CML, and major cytogenetic response occurred in 15% of patients. Omacetaxine showed activity in more advanced disease as well, with one of the 17 patients with accelerated-phase disease experiencing a complete cytogenetic response. Furthermore, T315I decreased in 57% of patients with chronic-phase CML, and the 2-year survival rate was 88%.

In a separate study conducted in 89 patients

for whom two or more tyrosine kinase inhibitors had failed, omacetaxine therapy resulted in complete hematologic responses and major cytogenetic responses in 82% and 23%, respectively, of 44 patients with chronic-phase CML; one patient with accelerated-phase CML achieved a partial cytogenetic response.¹¹⁸ Grade 3 or 4 myelosuppression, particularly thrombocytopenia, occurred in 71% of patients with chronic-phase disease.

Stem Cell Transplantation

Allogeneic stem cell transplantation is still considered to hold considerable curative potential in patients with CML. However, only 20–25% of patients are eligible for alloSCT, and the procedure is associated with a significant risk of morbidity and mortality, largely due to chronic graft-versus-host disease.^{35, 119} Five-year leukemia-free survival rates of 50–60% are achieved with alloSCT in patients with chronic-phase CML.^{119, 120} However, transplant-related mortality rates may be as high as 20–30%.¹²⁰ In a German CML study comparing the survival rates of patients with CML receiving human leukocyte antigen-identical sibling alloSCT with those of patients receiving hydroxyurea or IFN- α therapy, a significant survival advantage for hydroxyurea or IFN- α therapy was reported in the first 4 years after diagnosis.¹²⁰ However, a survival advantage for alloSCT could be discerned 5.5 years after diagnosis. A greater survival advantage with alloSCT was achieved in patients with intermediate-risk or high-risk prognostic features by Sokal criteria compared with those with CML characterized by low-risk features.

Moreover, best treatment outcomes with alloSCT in CML are achieved when patients undergo transplantation while in the chronic phase. Long-term survival decreases considerably when patients undergo transplantation while in the accelerated phase or in blast crisis. Thus, reserving transplantation until progression to the accelerated phase or blast crisis is less desirable since the outcome is not as beneficial as transplantation during chronic-phase CML.

In the pre-tyrosine kinase inhibitor era, alloSCT was considered as the preferred treatment modality in the front-line treatment of eligible patients who had a donor. However, compared with IFN-based treatment in 354 patients with chronic-phase CML, alloSCT was associated with inferior overall survival at a median follow-up of 8.9 years ($p=0.049$).¹¹⁹

Superiority with IFN-based therapy was most pronounced among patients who were at low risk for disease progression ($p=0.032$). These results suggest that alloSCT can no longer be considered the preferred option in all eligible patients but might be a reasonable option for specific patient subsets. However, the role of front-line alloSCT is questionable in the context of the improved clinical outcomes with tyrosine kinase inhibitor therapy and the increased risk of transplantation-related mortality and morbidity. Based on the results of IRIS and the above-mentioned trial comparing IFN-based treatment with alloSCT, until confirmatory data from randomized trials are available, it can be extrapolated that alloSCT might be inferior to imatinib therapy in newly diagnosed patients with CML.

Indeed, alloSCT is no longer indicated in the front-line setting but remains a second-line treatment option after imatinib failure or for patients who are unlikely to respond to further drug treatment and/or those in accelerated phase or blast crisis. A recent study determined that patients with anemia and high tumor burden are unlikely to respond to second-generation tyrosine kinase inhibitors and thus might be suitable candidates for alloSCT.¹²¹ Current clinical evidence indicates that previous treatment with imatinib does not negatively impact the clinical outcome of alloSCT. Although further studies are needed to establish the effect of second-generation tyrosine kinase inhibitor therapies on outcome of alloSCT, available data suggest that previous therapy with dasatinib or nilotinib does not increase transplantation-related toxicities.³⁹

In order to predict the outcomes of alloSCT, a European Group for Blood and Marrow Transplantation (EBMT) risk score was derived based on risk factors of disease phase, patient age, interval from diagnosis, donor type, and donor-recipient sex match from 3142 patients with CML treated with alloSCT (Table 14).³⁹ Although the EBMT risk score was defined before the introduction of tyrosine kinase inhibitors, it has not undergone substantial changes since then. For patients with risk scores of 0–2, 3–4, and 5–6, transplantation-related mortalities are 31%, 50% and 70%, respectively.³⁹

Practical Considerations

Managing Adverse Events

Myelosuppression is common in patients with CML treated with tyrosine kinase inhibitors, particularly in those with more advanced

Table 14. European Group for Blood and Marrow Transplantation Risk Score for Allogeneic Stem Cell Transplantation

Risk Factor	Risk Score
Disease phase	Chronic phase: 0 Accelerated phase: 1 Blast crisis: 2
Patient age	< 20 yrs: 0 20–40 yrs: 1 > 40 yrs: 2
Interval from diagnosis	≤ 1 yr: 0 > 1 yr: 1
Donor type	HLA-identical sibling: 0 Other: 1
Donor-recipient sex match	Female donor and male recipient: 1 Any other match: 0

HLA = human leukocyte antigen.

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disease.¹⁰³ In patients who are in blast crisis, myelosuppression usually begins in the first month, but in those with accelerated-phase or chronic-phase CML, its occurrence is delayed. Although grade 3 or 4 neutropenia is common, it rarely results in infectious complications. However, monitoring for myelosuppression is warranted, as 22 deaths have occurred in association with imatinib-induced myelosuppression. Management of myelosuppression should focus on avoiding potentially dangerous neutropenia and platelet transfusion dependence. Treatment interruption, but not dosage reduction, is the preferred course of action in patients in chronic-phase CML. In patients who are in blast crisis or have high-risk accelerated-phase CML, treatment interruptions or dosage reductions are not recommended; hematopoietic support with platelet transfusions is recommended in such instances. If significant bleeding occurs, imatinib should be withheld immediately until bleeding resolves. In some patients, the use of myeloid growth factors might be necessary.¹⁰³

Nonhematologic adverse events can also affect patient compliance. Gastrointestinal effects can be managed with antiemetics and antidiarrheal drugs.¹⁰³ Muscle cramps can be treated with calcium and magnesium supplements, whereas bone pain and arthralgias may respond to nonsteroidal antiinflammatory drugs or mild narcotic analgesics. Rashes can usually be controlled with antihistamines or topical steroids, and, in more severe cases, oral steroids. In some rare cases, Stevens-Johnson syndrome may occur, in which case imatinib therapy should be

discontinued immediately.¹⁰³

Edema and fluid retention are common toxicities of imatinib and dasatinib therapies.^{89, 103} Generalized edema, although less common, can be life-threatening, presenting as pulmonary edema, pleural or pericardial effusion, ascites, anasarca, or cerebral edema. Predisposing factors to edema include female sex, age older than 65 years, and a history of cardiac or renal insufficiency. Thus, in older patients or those with a history of cardiac or renal insufficiency, therapy should be initiated with imatinib 300 mg/day and increased to 400 or 600 mg/day as tolerated.¹⁰³ Patients should be monitored for signs of peripheral edema or rapid weight gain. Diuretic therapy should be initiated as soon as edema is evident. In those with severe fluid retention, imatinib should be discontinued and the edema controlled with diuretics. Imatinib may be started again, but diuretic therapy should be maintained. Fluid retention events, such as weight gain, edema, and pleural and pericardial effusions, are rare with nilotinib therapy.¹²²

Pregnancy

Tyrosine kinase inhibitor therapies are generally better tolerated and more efficacious than historical treatment approaches, and due to these reasons, tyrosine kinase inhibitor therapy is considered an integral part of the chronic management of the disease. In this context, addressing quality-of-life issues such as fertility and pregnancy are a practical necessity. Due to concerns of impaired fertility related to therapy, patients should consider cryopreservation of semen and oocytes. In order to maintain disease control, interruption of tyrosine kinase inhibitor therapy in chronic-phase CML is not recommended. Existing clinical evidence suggests that children born to men taking imatinib therapy at the time of conception are not at greater risk for abnormalities, thus discontinuation of imatinib is not recommended in these patients.¹²³ However, there is some evidence that rare congenital abnormalities can occur in women exposed to imatinib therapy during pregnancy. In particular, treatment during the first trimester is associated with the greatest risk for congenital malformations. Alternative strategies for management of CML during pregnancy include regular leukopheresis and/or IFN- α . No data exist, to our knowledge, on the use of nilotinib or dasatinib during pregnancy. Moreover, imatinib and its metabolites are found in the milk of lactating rats, as are dasatinib and nilotinib.¹²³

Conclusion

The advent of imatinib for the front-line treatment of CML has significantly improved clinical outcomes and changed the natural history of the disease. However, a third of patients either fail to respond or respond suboptimally to imatinib therapy, and others are intolerant to imatinib. An increased understanding of the molecular basis of imatinib resistance has led to rational development of second-generation tyrosine kinase inhibitors as second-line treatment options for imatinib-resistant patients. Dasatinib and nilotinib have demonstrated significant single-agent activity and are associated with favorable safety profiles in patients with CML. It is recommended that the selection of a second-generation tyrosine kinase inhibitor to rescue patients with imatinib failure be based on several factors, including age, comorbidities, ABL kinase mutational profile, historical responses, and toxicity profiles of the drug. Molecular monitoring is a powerful tool that is often used to guide clinicians with treatment decisions in the clinic. A growing body of evidence suggests that second-generation tyrosine kinase inhibitors may eventually replace imatinib as the standard of care for patients with newly diagnosed CML.

Persistence of minimal residual disease and development of targeted agents against the T315I mutation are proving to be formidable challenges. In this context, treatment options are evolving for patients with CML, with several novel agents such as bosutinib, omacetaxine mepesuccinate, and AP24534 showing promising activity in patients with CML, even in those with the T315I mutation. Longer follow-up of ongoing trials will better define the role of these emerging agents in the management of patients with CML. Autologous stem cell transplantation remains the only curative option, but the high morbidity and mortality associated with the procedure make it a less attractive option than current tyrosine kinase inhibitor therapy. However, autologous stem cell transplantation has an important role as salvage therapy in patients who have failed to respond to tyrosine kinase inhibitor therapy.

Careful management of adverse events can improve patient safety and outcomes, as patients are more likely to be compliant with therapy if adverse effects are controlled. Use of diuretics for edema, and antiemetics and antidiarrheal agents for gastrointestinal effects can help patients continue with therapy and achieve a better quality of life. Other quality-of-life issues,

such as preserving fertility and continuing tyrosine kinase inhibitor therapy during pregnancy, have also risen to the forefront.

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