Current and Emerging Treatment Options in Chronic Myeloid Leukemia

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Treatments for chronic myeloid leukemia (CML) represent a success story in molecular medicine. The development of imatinib, a tyrosine kinase inhibitor (TKI) targeted against the causative Bcr-Abl oncoprotein in CML, has resulted in hematologic and cytogenetic remissions in all phases of CML. A significant proportion of patients are resistant to imatinib or develop resistance during treatment. This is often a result of mutated forms of the Bcr-Abl oncoprotein to which imatinib is unable to bind. Several strategies have been developed to overcome the problem of imatinib resistance, including high-dose imatinib, novel targeted agents, and combination treatments. Novel agents include dasatinib, a potent TKI that inhibits several critical oncogenic proteins and which has recently been approved for patients with CML who are resistant or intolerant to imatinib; and nilotinib, a potent selective Bcr-Abl kinase inhibitor currently in clinical development. Other agents in development include SKI-606 and INNO-406. Stem cell transplantation remains a useful option, although it is not generally used as first-line treatment. Overall, there are an increasing number of treatment options available for patients with CML. ***Cancer* 2007;109:2171–81.** © *2007 American Cancer Society.*

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Chronic myeloid leukemia (CML) is one of the most extensively studied and, arguably, best understood neoplasms.[1–4] Approximately 4500 new cases of CML are diagnosed in the U.S. each year, accounting for 13% of all leukemia diagnoses.[5] The cytogenetic hallmark of CML is the Philadelphia chromosome (Ph), created by a reciprocal translocation between chromosomes 9 and 22 (t[9;22][q34;q11]). The conjugation of the breakpoint cluster region gene on chromosome 22 and the Abelson kinase gene on chromosome 9 creates the *BCR-ABL* oncogene, which codes for a deregulated tyrosine kinase. Bcr-Abl activates multiple signal transduction pathways, including Ras/Raf/mitogen-activated protein kinase (MAPK), phosphatidylinositol 3 kinase, STAT5/Janus kinase, and Myc. Bcr-Abl activity leads to uncontrolled cell proliferation and reduced apoptosis, resulting in the malignant expansion of pluripotent stem cells in bone marrow.

CML normally progresses through 3 clinically recognized phases. Approximately 90% of patients are diagnosed during the typically indolent chronic phase (CP), which is followed by an accelerated phase (AP) and a terminal blastic phase (BP). Although progression through all stages is most common, 20% to 25% of patients progress directly from CP to BP. The time course for progression can also be extremely varied. The mechanisms behind CML disease progression are not fully understood. As patients progress through the different phases, cytogenetic abnormalities may be detected in addi-

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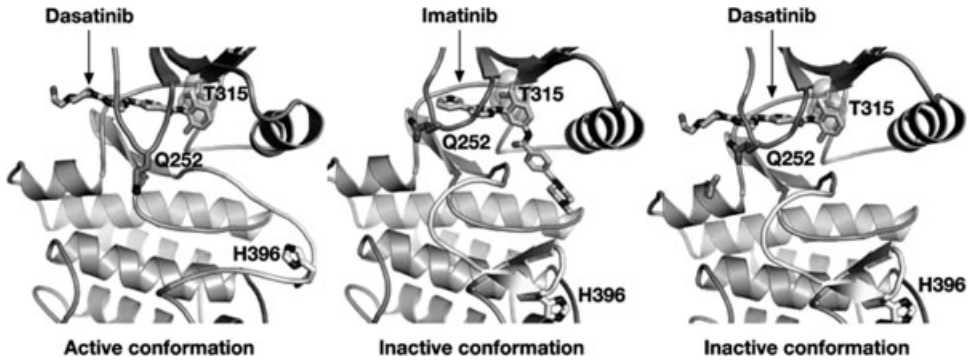

FIGURE 1. Binding of imatinib and dasatinib to the ATP-binding site of the ABL kinase domain of BCR-ABL. Unlike imatinib, dasatinib binds both the active and inactive conformations of the protein. Reproduced with permission from Jabbour E, Cortes J, Giles F, O'Brien S, Kantarjian H. The clinical challenge of imatinib resistance in chronic myeloid leukemia: emerging strategies with new targeted agents. *Targ Oncol.* 2006;1:186–196. © Springer-Verlag France.

tion to the Ph chromosome (termed clonal evolution). Mutations and deletions in specific genes may also occur (eg, *p53*, *p16/INK4a*, and *RB*). Increasing evidence suggests that Src family kinases may be involved in CML disease progression through the induction of cytokine independence and apoptotic protection.[6–8]

Historically, CML was treated with conventional busulfan or hydroxyurea chemotherapy and was associated with a poor prognosis.[3,9] Although these agents controlled hematologic manifestations of the disease, they did not delay disease progression. Treatment with interferon-α (IFN-α) represented a significant advance, producing hematologic and cytogenetic responses in patients with CP CML, and improving survival compared with previous treatments (5-year survival rate of 57% for IFN-α compared with 42% for chemotherapy; $P < .00001$).[10] Combining cytarabine (a DNA synthesis inhibitor) with IFN-α was found to produce additional benefits.[11,12] Hematopoietic stem cell transplantation (SCT) also remains a useful treatment for some patients. The current first-line therapy for CML is imatinib.

Imatinib Mesylate

Imatinib mesylate (Gleevec®/Glivec®; Novartis, Basel, Switzerland) is an orally available, small-molecule tyrosine kinase inhibitor (TKI), and was the first therapy designed to selectively target the causative *BCR-ABL* oncogene in CML.[13] Imatinib also inhibits other signaling proteins, including platelet-derived growth factor receptor (PDGFR) and Kit,[14] but not other tyrosine kinases such as Src family kinases. Imatinib acts by binding to the inactive form of Bcr-Abl, preventing a conformational switch to the active form of the oncoprotein, and also by partially occluding the enzyme's ATP binding site (Fig. 1). This prevents Bcr-Abl autophosphorylation, interfering with its activation and blocking signal transduction.

The efficacy of imatinib was demonstrated in the Phase III IRIS (International Randomized Study of Interferon and STI571) trial, in which imatinib given at a dose of 400 mg daily was compared with the combination of IFN-α and cytarabine (a previous treatment option) in patients with newly diagnosed CP CML (n = 1106).[15] After a median follow-up of 19 months, imatinib was found to be significantly better than the IFN-α–based treatment, as shown by rates of complete hematologic response (CHR) (95% vs 56%; $P < .001$) and major cytogenetic response (MCyR)($\leq$35% Ph-positive [Ph^+] cells in metaphase; 85% vs 22% [$P < .001$]) (see Table 1 for definitions). Major molecular response (MMR) rates and progression-free survival were also found to be superior with imatinib.[15,16] Best responses after 5 years of follow-up are shown in Table 2.[17] Adverse events (AEs) associated with imatinib were generally mild or moderate, and included superficial edema, nausea, muscle cramps, and rashes (according to the common terminology criteria rare version 3.0). Grade 3–4 events were uncommon except for neutropenia (14%) and thrombocytopenia (8%).[15] Recently, imatinib was reported to be associated with cardiotoxicity and congestive heart failure,[18] although this appears to be uncommon in clinical practice.[19]

Imatinib resistance

Some patients are intrinsically resistant to imatinib (primary resistance), and others may acquire resistance during treatment (secondary resistance [ie, imatinib treatment benefit is lost after an initial response]).[3] Imatinib resistance is defined using several clinical, hematologic, or molecular criteria (Table 3). Both

TABLE 1
Definitions of Endpoints used in CML Trials

Complete hematologic response	White blood cell count < 10,000 per mm^3
	Absolute neutrophil count ≥ 1000/mm^3 (AP or BP disease)
	Platelet count < 450,000/mm^3 (CP disease)
	Platelet count ≥ 100,000/mm^3 (AP or BP disease)
	< 5% myelocytes plus metamyelocytes
	< 2% basophils
	Absence of blasts and promyelocytes
	Absence of extramedullary involvement
Complete cytogenetic response (CCyR)	0% Ph^+ cells in metaphase in a bone marrow sample
Partial cytogenetic response (PCyR)	1–35% Ph^+ cells in metaphase in a bone marrow sample
Major cytogenetic response	CCyR and PCyR (ie, ≤ 35% Ph^+ cells in metaphase in a bone marrow sample)
Minor cytogenetic response	36–65% Ph^+ cells in metaphase in a bone marrow sample
Major molecular response	Reduction in *BCR-ABL* transcript levels in peripheral blood by ≥ 3 log or *BCR-ABL/ABL* ratio reduced to ≤ 0.1%
Complete molecular response	*BCR-ABL* transcripts undetectable

CML indicates chronic myeloid leukemia; AP, accelerated phase; BP, blastic phase; CP, chronic phase; Ph^+, Philadelphia chromosome-positive.

TABLE 2
Best Observed Responses at 5 Years in Patients Remaining on First-Line Imatinib Therapy in the Phase III IRIS Trial.[17]

Parameter	Percentage of patients
Complete hematologic response	97
Major cytogenetic response	89
Complete cytogenetic response	82
Survival	
Overall	89
Excluding non-CML deaths	95
Survival without accelerated or blastic phase	93
Event-free survival	83

IRIS indicates International Randomized Study of Interferon and STI571 trial; CML, chronic myeloid leukemia.

intrinsic and acquired resistance are more common in patients with advanced phases of disease. In a study of 300 patients followed for 4.5 years from a single center, the percentages of patients in CP, AP, or myeloid BP failing to achieve a CHR after initial imatinib treatment (intrinsic resistance) were 3%, 9%, and 51%, respectively. The percentages of patients experiencing hematologic recurrence after an initial response (acquired resistance) were 22%, 32%, and 41%, respectively.[20]

The recent update from the IRIS study provides a separate indication of imatinib resistance.[17] After 5 years, 31% of patients (171 of 553 patients) initially receiving imatinib had discontinued first-line treatment (including 4% for AEs, 11% for unsatisfactory therapeutic effect, and 2.5% to cross over to IFN-α treatment). When best observed response rates in patients remaining on treatment are incorporated (97% CHR rate and 89% MCyR rate), approximately 33% of imatinib-treated patients had not achieved a CHR and 39% had not achieved a MCyR.

Various mechanisms may contribute to imatinib resistance, including increased expression of Bcr-Abl kinase through gene amplification, decreased intracellular imatinib concentrations caused by drug efflux proteins, imatinib binding by plasma proteins, and clonal evolution.[3] In addition, Lyn and Hck are overexpressed in some imatinib-resistant patient isolates and cell lines, suggesting that Src family kinases may be involved in Bcr-Abl independence and progression to imatinib resistance.[6–8] However, approximately 35% to 45% of cases of imatinib resistance arise because of mutations in the *BCR-ABL* kinase domains.[20,21] Clinically relevant *BCR-ABL* mutations disrupt critical contact points between imatinib and the Bcr-Abl protein or induce structural alternations that prevent imatinib binding, often by inducing a transition from the inactive to the active conformation of the protein, to which imatinib is unable to bind.[3,22] With continued imatinib treatment, resistant mutants are selected that eventually outgrow drug-sensitive leukemic cells. The number of different *BCR-ABL* mutations identified has steadily increased.[22] Clusters of mutations have been described in several areas of the Bcr-Abl molecule, including the ATP binding site (P-loop), imatinib binding site, activation loop (controlling kinase activation), and catalytic domain. Some Bcr-Abl mutations result in a highly resistant phenotype in vitro; others remain relatively sensitive, meaning that resistance can be overcome by increasing the imatinib dose. Higher rates of mutations are detected with increasing transcript levels (eg, 2–5 fold), failure to achieve a MCyR, and more advanced disease.[23,24] Mutations in the P-loop

TABLE 3
Imatinib Resistance Definitions in Clinical Studies of Dasatinib in Patients with CP CML

CML phase		Hematologic	Cytogenetic
Chronic	Acquired	Loss of CHR on all assessments over a consecutive 2-week period Continuously increasing WBC on at least 2 consecutive evaluations at least 2 weeks apart, with final assessment showing a doubling from the nadir to $\geq$20,000/mm^3 or an absolute increase in WBC by >50,000 mm^3 above lowest count after imatinib	Loss of MCyR and increased Ph$^+$ metaphases by 30% on 2 occasions at least 4 weeks apart
	Intrinsic	No CHR after 3 mo of imatinib	No CyR after 6 mo of imatinib No MCyR after 12 mo of imatinib

CP indicates chronic phase; CML indicates chronic myeloid leukemia; CHR, complete hematologic response; WBC, white blood cell count; MCyR, major cytogenetic response; Ph+, Philadelphia chromosome-positive; CyR, cytogenetic response.

may be associated with a poor prognosis,[23,25,26] although this was not confirmed in a separate analysis.[24]

High-dose imatinib

Imatinib dose escalation is an accepted clinical strategy for overcoming resistance. In patients with resistance or disease recurrence after imatinib at a dose of 300 or 400 mg/day, doubling the dose achieved hematologic or cytogenetic responses in greater than half of patients.[27] An improved level of efficacy was achieved with higher starting doses (600 or 800 mg/day) in Phase II trials of patients with AP or BP CML.[28,29] High-dose (HD) imatinib (800 mg/day) has been evaluated as first-line therapy in newly diagnosed CP CML patients. Responses in 175 patients (with a median follow-up of 30 months) were compared with historical controls (n = 50) receiving standard-dose (SD) imatinib (median follow-up of 53 months).[30,31] Overall, 90% of HD-treated patients achieved a complete cytogenetic response (CCyR) compared with 78% of those receiving SD imatinib ($P = .03$). The MMR rate at 12 months was 54% versus 24% with SD, respectively ($P = .001$), and complete molecular remission rates (undetectable levels of *BCR-ABL* transcripts) at 24 months were 27% and 10%, respectively. Some investigators have questioned the durability of responses after imatinib dose escalation.[32,33] As discussed above, dose escalation is likely to be useful only in a subset of patients with imatinib resistance (cytogenetic relapse). Alternative treatment options are required for other patients.

New and Emerging Targeted Agents for CML

Several novel CML therapies have been designed to inhibit wild-type and mutant forms of Bcr-Abl and other molecular targets. One agent (dasatinib) has been approved for clinical use, and others (eg, nilotinib/AMN107) are likely to follow. These novel agents are now discussed.

Dasatinib

Dasatinib (SPRYCEL®; Bristol-Myers Squibb, New York, NY) has recently been approved by the U.S. Food and Drug Administration (FDA) for the treatment of adults with CP, AP, or myeloid or lymphoid BP CML with resistance or intolerance to prior therapy including imatinib. Dasatinib is also indicated for the treatment of adults with Ph$^+$ acute lymphoblastic leukemia with resistance or intolerance to prior therapy. Dasatinib is a novel, orally available, multitargeted, potent TKI that inhibits several critical oncogenic proteins, including Bcr-Abl, Src family of kinases, Kit, PDGFR, and ephrin A receptor kinase.[34–37] The structure of dasatinib is based on a different chemical scaffold to imatinib. Dasatinib has a 325-fold greater potency than imatinib for wild-type Bcr-Abl[38] and, unlike imatinib, binds both the inactive and active conformations of the protein (Fig. 1).[39] Dasatinib effectively inhibits all imatinib-resistant kinase domain mutations tested, with the exception of T315I.[38,40] Src family kinase inhibition in Bcr-Abl-expressing cells induces growth arrest and apoptosis,[41,42] suggesting that the wider target range of dasatinib has the potential to provide additional treatment benefits compared with more specific agents.

Unlike imatinib, dasatinib is not a substrate of multidrug resistance protein-1 (MDR1), an efflux protein expressed on normal and leukemic hematopoietic stem cells.[43,44] Efflux proteins might prevent adequate intracellular concentrations of imatinib being reached and may partly explain imatinib insensitivity.[45] Dasatinib may target an earlier progenitor population than imatinib in CML patient isolates, although the most primitive quiescent cells may be inherently resistant to both drugs.[46]

TABLE 4
Summary of Outcomes from the Dasatinib Phase II Clinical Development Program

Disease	Minimum follow-up, months	No.	Response rate (Percentage of patients) CHR		MCyR		CCyR		Study name
CP CML	8	186	90		52		39		START-C*[48]
AP CML	8	107	39		33		24		START-A*[49]
BP CML	8	116	26		38		33		START-B and -L*[50]
Ph^+ ALL	8	46	35		57		54		START L*[51]
CP CML	15**	150	D	IM	D	IM	D	IM	START-R†[52]
			93	82	52	33	40	16	

CHR indicates complete hematologic response; MCyR, major cytogenetic response; CCyR, complete cytogenetic response; CP, chronic phase; CML, chronic myeloid leukemia; AP, accelerated phase; BP, blastic phase; Ph^+, Philadelphia chromosome-positive; ALL, acute lymphoblastic leukemia; **, median follow-up; D, dasatinib; IM, imatinib.

* Single-arm open-label trials.

† Double-arm randomized trial.

Dasatinib has been clinically assessed in 1 dose-finding study and 5 subsequent studies involving greater than 900 imatinib-resistant or imatinib-intolerant patients (the START program). Phase I data suggested that dasatinib was associated with a high level of efficacy and durability.[47] Results from the START program demonstrated that treatment with dasatinib at a dose of 70 mg twice daily resulted in hematologic and cytogenetic responses across all phases of CML in both imatinib-intolerant and imatinib-resistant patients (Table 4).[48–52] In particular, dasatinib was associated with molecular responses in patients with imatinib-resistant/intolerant CML and multiple Bcr-Abl mutations.[53] Response rates were similar regardless of whether patients had Bcr-Abl mutations within the kinase domain.

Because dasatinib has higher potency than imatinib in vitro, it is of interest to compare this agent with HD imatinib treatment. This was the purpose of START-R, a randomized Phase II trial in patients with CP CML and treatment failure after SD imatinib (400–600 mg daily). Patients were randomized 2:1 to receive either oral dasatinib at a dose of 70 mg twice daily or imatinib at a dose of 400 mg twice daily (n = 150 patients). Data from a median follow-up of 15 months demonstrated that dasatinib was associated with higher response rates than HD imatinib.[52] A MCyR was achieved in 52% of patients treated with dasatinib versus 33% of imatinib-treated patients and a CHR was observed in 93% versus 82% of patients, respectively. In particular, a CCyR was achieved in 40% versus 16% of patients, respectively, indicating a greater depth of response for dasatinib compared with HD imatinib. In patients with no prior cytogenetic response to imatinib therapy, MCyRs occurred in 49% of dasatinib-treated patients compared with 7% of those receiving HD imatinib. There was a higher rate of myelosuppression and pleural effusion with dasatinib. These data suggest that dasatinib has the potential to delay disease progression to a greater extent than HD imatinib.

Throughout the START program, dasatinib was generally well tolerated, with drug-related serious AEs normally resolving after dose reduction or interruption.[48–52] Imatinib-intolerant patients remained on dasatinib longer than imatinib-resistant patients and did not experience Grade 3–4 cross-intolerance. Grade 3–4 thrombocytopenia, and neutropenia occurred in nearly 50% of patients. Nonhematologic AEs were generally mild to moderate. Pleural effusions were observed in 5% to 35% of dasatinib-treated patients (severe in 3–15% of patients), although the highest incidence was noted in patients in advanced phases of CML. With early recognition and appropriate measures (dose adjustments, steroids, and diuretics), pleural effusions can be effectively controlled.

Nilotinib

Nilotinib (AMN107, Novartis, Basel, Switzerland) is an orally administered derivative of imatinib currently in clinical development that inhibits Bcr-Abl with a 30- to 50-fold greater potency than imatinib.[38] Similar to imatinib, nilotinib binds Bcr-Abl in its inactive conformation only. Nilotinib has demonstrated activity against nearly all Bcr-Abl mutants tested, although similar to dasatinib (and imatinib), nilotinib is unable to inhibit the T315I mutation. Nilotinib also inhibits PDGFR and Kit, but unlike dasatinib, it does not inhibit Src family of kinases.

In a Phase I dose escalation study (n = 119 patients), nilotinib demonstrated activity in patients with imatinib-resistant CML.[54] Nilotinib has also been examined in 3 ongoing Phase II studies in patients with CML and imatinib resistance or intolerance, and data are currently available from 326 patients who received nilotinib at a dose of 400mg twice daily.[55–57] The clinical activity of nilotinib was observed in all phases of CML; CHRs were recorded in 74%, 25%, and 13%, respectively, of patients with CP, AP, and BP disease (Table 5). MCyRs were recorded in 52% and 36% of CP and AP patients, respectively. CHRs were observed in 6% of patients with recurrent/refractory Ph^+ acute lymphoblastic leukemia (ALL).

Overall, nilotinib treatment was associated with a very favorable safety and tolerability profile. Frequently reported AEs in Phase I and II studies were myelosuppression (Grade 3–4 in 10–20% of patients),

mild-to-moderate rashes, pruritus, nausea, and peripheral edema.[54–57]

Other targeted therapies in development

Several other Bcr-Abl inhibitors are currently in preclinical or early clinical development (Table 6).[58–68] Similar to dasatinib, several of these agents have activity against both Bcr-Abl and Src family kinases, and therefore have the potential for greater clinical activity in CML. Two novel agents, bosutinib (SKI-606) and INNO-406 (NS-187), have reached Phase I–II trials. None of the agents discussed thus far are capable of inhibiting the T315I mutant of Bcr-Abl. However, MK-0457 (previously VX-680), an ATP-competitive small molecule discovered as an aurora kinase inhibitor, inhibits Bcr-Abl kinase activity and in vitro proliferation of cells expressing T315I.[67] A recent study has demonstrated clinical responses to MK-0457 in 3 patients carrying the T315I mutation.[68] ON012380, a non-ATP-targeted agent, has also shown activity against imatinib-resistant Bcr-Abl mutants, including T315I, both in vitro and in vivo.[58]

Targeting pathways downstream of Bcr-Abl may provide an alternative therapeutic strategy in CML. The Ras signaling pathway is downstream of Bcr-Abl in CML cells, and inhibition of farnesyl transferase activity blocks Ras activation.[2,69] Two orally administered farnesyl transferase inhibitors, lonafarnib (SCH66336) and tipifarnib (R115777), have been associated with hematologic and cytogenetic responses in pilot studies in CML.[70–72]

Combination strategies

Another approach for treating CML is to combine imatinib with a different agent, including other targeted therapies. In vitro studies have shown combination with the Bcr-Abl/Src inhibitors dasatinib or AP23464 enhanced imatinib's activity for inhibiting phosphorylation of wild-type Bcr-Abl. In addition, imatinib did not appear to interfere with the inhibition of resistant Bcr-Abl mutants, although no effect was observed on T315I.[73] In early clinical studies in patients with CML and imatinib treatment failure, combined treatment with imatinib and either lonafarnib or tipifarnib was associated with hematologic and cytogenetic responses in all 3 phases of CML disease.[74] It is interesting to note that lonafarnib reduces the imatinib resistance of primitive quiescent CML cells, which may result in part from the ability of lonafarnib to inhibit the MDR1 efflux pump found in leukemic stem cells.[75] Combination strategies involving imatinib and other agents currently are under investigation, including homoharringtonine (a plant alkaloid that inhibits protein synthesis and induces apoptosis), decitabine (a hypomethylating agent), and suberoylanilide hydroxamic acid (a histone deacetylase inhibitor).[74,76]

TABLE 5
Summary of Outcomes from Nilotinib Phase II Trials*

Disease	Minimum follow-up, months	No.	Response rate (Percentage of patients)		
			CHR	MCyR	CCyR
CP CML[55]	6	280	74	52	34
AP CML[56]	8	64	25	36	22
BP CML[57]	NR	96	13	NR	NR
Ph^+ ALL[57]	NR	34	6	NR	NR

CHR indicates complete hematologic response; MCyR, major cytogenetic response; CCyR, complete cytogenetic response; CP, chronic phase; CML, chronic myelogenous leukemia; AP, accelerated phase; BP, blastic phase; NR, not reported; Ph^+, Philadelphia chromosome-positive; ALL, acute lymphoblastic leukemia.

* Data updated from the ASH presentations.

Stem Cell Transplantation

Because of the success of Bcr-Abl inhibitors, allogeneic SCT has changed from being a preferred first-line therapy to a second-line or third-line option. Despite this, SCT remains an important treatment that offers the potential for cure, although this needs to be

TABLE 6
Emerging Tyrosine Kinase Inhibitors with Potential in CML

Agent	Targets	Stage of development	Reference
Bosutinib (SKI-606)	Abl, Src	Phase I/II	Golas et al., 2003[64] and Cortes et al., 2006[65]
MK-0457	Abl, aurora kinases	Phase I	Carter et al., 2005[67] and Giles et al., 2007[68]
INNO-406 (NS-187)	Abl, Lyn	Phase I	Kimura et al., 2005[59]
AZD0530	Abl, Src	Phase I (solid tumors, not CML)	Hennequin et al., 2005[61] and Lockton et al., 2005[62]
AP23464	Abl, Src	Preclinical	O'Hare et al., 2004[60]
ON012380	Abl	Preclinical	Gumireddy et al., 2005[58]
PD166326	Abl, Src	Preclinical	Wolff et al., 2005[63]

CML indicates chronic myeloid leukemia.

balanced with the possible risks, which include mortality, graft-versus-host disease, life-threatening infections, and the risk of secondary malignancy.[77] Prior imatinib treatment does not appear to adversely affect SCT.[78] Recent reports provide the best estimates of current outcomes after SCT. Data were analyzed from 131 CP CML patients undergoing SCT (bone marrow or peripheral blood) from related donors at a single institution in the U.S. between 1995 and 2000.[79] The estimated probability of disease-free survival at 3 years was 78%, with survival and disease recurrence rates estimated at 86% and 8%, respectively. The Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT) has recently provided updated data.[80] Among all European patients undergoing SCT for CML between 2000 and 2003 (n = 3018), the 2-year survival rate was 61%, the transplant-related mortality rate was 30%, and the rate of disease recurrence was 22%. However, better outcomes were observed in patients who underwent SCT at the time of first CP from a human leukocyte antigen (HLA)-identical sibling (2-year survival rate of 74%, transplant-related mortality rate of 22%, and disease recurrence rate of 18%). These data illustrate that outcome after SCT is highly dependent on defined risk factors. In the EBMT study, favorable risk factors were sibling donor, treatment at an early stage of disease, younger recipient age (age < 20 years vs ages 20–40 years vs age > 40 years); and < 12 months from the time of diagnosis to SCT.[80,81] If successful, SCT can have long-term results. In a 10-year study of patients receiving allogeneic bone marrow from siblings (46 in first CP, and 43 in advanced phases), the mean time to hematologic or cytogenetic disease recurrence was 7.7 years and 46% of the long-term survivors (13 of 28 patients) never developed disease recurrence.[82]

Because as many as two-thirds of patients do not have a suitable HLA-matched sibling, SCT from unrelated HLA-matched donors has been examined. One study compared results from 2464 unrelated donor bone marrow transplantations with 450 HLA-identical sibling donor transplantations performed at National Marrow Donor Program institutions in the U.S. between 1988 and 1999.[83] In the unrelated donor group, 63% were matched at HLA-A, HLA-B, and HLA-DRB1 alleles. Multivariate analysis demonstrated a significantly increased risk of graft failure and acute graft-versus-host disease after transplantation from an unrelated donor compared with a related donor, and survival and disease-free survival were found to be significantly worse for patients who received SCT from unrelated donors. However, for patients with CP CML undergoing transplantation within 1 year from diagnosis, the 5-year disease-free survival rate was similar or only slightly inferior.

Immunotherapy for CML

Targeting CML with vaccines is an attractive option to potentially eradicate minimal residual disease, and several approaches are currently in early clinical development. The junction between the fused *BCR* and *ABL* genes in CML creates a novel peptide sequence that is unique to leukemic cells. In 2 trials of junction peptide-based vaccination, peptide-specific T-cell responses and clinical responses were observed, including improved cytogenetic responses and transient undetectable levels of *BCR-ABL* transcripts.[84,85] Vaccination with autologous tumor-derived heat shock proteins, which are immunogenic and likely to contain tumor-specific peptides, also has resulted in improved cytogenetic or molecular responses in some patients.[86,87] Clinical effects have been associated with other immunotherapy strategies, including vaccination with the PR1 peptide derived from proteinase 3,[88] and a K562 cell-based vaccine expressing granulocyte-macrophage–colony-stimulating factor.[89]

Disease Monitoring in CML and Residual Disease

In the imatinib era, more sophisticated methods have been developed for monitoring disease status and treatment response in patients with CML. After initial treatment, hematologic and cytogenetic responses are most informative. In patients achieving a CCyR, residual disease is assessed by measuring the molecular response (ie, levels of *BCR-ABL* transcripts in peripheral blood or bone marrow) using reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR).[90,91] Early *BCR-ABL* measurements in peripheral blood or bone marrow are predictive of subsequent cytogenetic response.[92] In addition, achieving a MMR (*BCR-ABL*:control gene ratio reduced to 0.1%) after imatinib treatment has prognostic significance. In 2 studies, achieving a MMR within 12 months was associated with significantly longer durations of cytogenetic disease remission.[93,94] In another trial, significant increases in progression-free survival (measured at 16.5 months) could be predicted by molecular responses to imatinib at 4 weeks ($P = .01$) or 3 months ($P = .003$), and these effects were found to be independent of patient age and disease stage.[95] In the IRIS study, 100% of patients achieving a CCyR and MMR at 18 months with imatinib were free of disease progression at 5 years, compared with 98% who achieved a CCyR but not a MMR.[17]

A complete molecular response (CMR) (ie, undetectable *BCR-ABL* transcripts) may be useful for predicting long-term response. Because the sensitivity of detection may vary between centers, results should be interpreted with caution. In 1 study of 59 patients with a CCyR after imatinib treatment, none of the 16 patients achieving an undetectable *BCR-ABL* level experienced a cytogenetic disease recurrence, whereas disease recurrence was observed in 30% of patients without a CMR (13 of 43 patients) (median follow-up of 43 months).[96] Factors that were predictive of CMR were CCyR at 3 months ($P = .024$) or 6 months ($P = .038$). Although CMR indicates an extremely low level of residual disease, studies have shown that this does not represent "cure." Across several reports, imatinib treatment has been discontinued in 32 patients after achieving a CMR.[97–102] Of these, 13 of 32 patients (41%) continued to demonstrate a CMR without treatment, whereas 19 of 32 patients (59%) experienced disease recurrence, which often occurred shortly after treatment cessation.

An important part of molecular monitoring is to identify mutations in *BCR-ABL*, which may signal imatinib resistance.[90,91] Alternative therapies can then be considered at the earliest opportunity.

CONCLUSIONS

Imatinib has provided treatment benefits for a large number of patients with CML. However, imatinib resistance represents a significant clinical problem that may not be overcome by an increase in dose. Novel treatment strategies have been investigated in patients with CML and a failure of imatinib therapy. Dasatinib, a novel agent targeting multiple kinases, has demonstrated efficacy in patients with imatinib intolerance or resistance and is now available. Nilotinib, a novel derivative of imatinib, has shown promise in clinical trials. Both agents have the potential to be effective in patients whose disease is caused by mutated forms of Bcr-Abl that do not respond to imatinib. Although SCT remains an important treatment option that may cure CML, it is now often used as second-line or third-line therapy after the failure of imatinib and second-generation TKIs. Other strategies currently are in clinical development, including combination treatments and immunotherapy. Overall, treatment options are increasing for patients with CML, and this is likely to continue in the future.

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