

Dasatinib in the treatment of imatinib refractory chronic myeloid leukemia

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Abstract: The development of imatinib for the treatment of chronic myeloid leukemia (CML) has proven to be an example of medical success in the era of targeted therapy. However, imatinib resistance or intolerance occurs in a substantial number of patients. Additionally, patients who have progressed beyond the chronic phase of CML do relatively poorly with imatinib therapy. Mechanisms of imatinib resistance include BCR-ABL point mutations resulting in decreased imatinib binding, as well as mutation-independent causes of resistance such as SRC family kinase dysregulation, BCR-ABL gene amplification, drug influx/efflux mechanisms and other poorly understood processes. The options for therapy in these patients include stem cell transplantation, imatinib dose escalation as well as the use of second-generation tyrosine kinase inhibitors. Dasatinib is a second-generation multi-kinase inhibitor with several theoretical and mechanistic advantages over imatinib. Moreover, several studies have evaluated dasatinib in patients who have progressed on imatinib therapy with encouraging results. Other novel agents such as mTOR inhibitors, bosutinib and INNO 406 have also shown promise in this setting. Although treatment options have increased, the choice of second-line therapy in patients with CML is influenced by concerns surrounding the duration of response as well as toxicity. Consequently, there is no agreed upon optimal second-line agent. This paper reviews the current data and attempts to address these issues.

Keywords: chronic myeloid leukemia (CML), dasatinib, imatinib, resistance (imatinib resistance), nilotinib, tyrosine kinase inhibitor

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder with an incidence of ~1 to 2 cases per 100,000 adults which is characterized by the presence of a balanced translocation between chromosomes 9 and 22 termed the Philadelphia chromosome.^{1,2} The molecular consequence of this translocation is the creation of a novel fusion gene (BCR/ABL) and its transcript protein. This protein is a constitutively active tyrosine kinase resulting in abnormal clonal expansion of the myeloid hematopoietic lineage. CML has a triphasic course with 90% of patients presenting in the chronic phase of disease.³ In time, without treatment there will be evidence of progression into the accelerated phase and ultimately into blast crisis which is typified by a lack of myeloid differentiation.

A phase 3 randomized study has demonstrated that the tyrosine kinase inhibitor, imatinib mesylate, produces major improvements in cytogenetic and hematologic response rates, as well as improvements in progression-free survival compared with interferon alfa and cytarabine.⁴ Imatinib inhibits BCR-ABL as well as C-kit and PDGFR kinases. However, only a fraction of imatinib-treated patients were able to achieve disease eradication at the molecular level (4%) and therapy must be continued indefinitely.^{5,6} Moreover, 31% of patients in the imatinib arm were unable to continue therapy due to intolerance or progressive disease.⁴ The event-free survival at 60 months of

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follow-up was 83% and 6% of these patients had progressed to the accelerated phase or blast crisis.⁴

Additionally, patients who had progressed beyond the chronic phase of CML do relatively poorly. After 4 years of imatinib therapy 75% of patients treated with imatinib in accelerated phase and 95% of patients diagnosed in blast crisis had developed resistance.⁵ Mechanisms of imatinib resistance include BCR-ABL point mutations resulting in decreased imatinib binding, as well as mutation independent causes of resistance such as Src family kinase dysregulation, BCR-ABL gene amplification, drug influx/efflux mechanisms and other poorly understood processes.^{1,5,7}

The role of imatinib has also been evaluated in patients with Philadelphia chromosome positive acute lymphoblastic leukemia (ALL). Encouraging results were noted in patients with Philadelphia positive ALL (Ph+ ALL) utilizing combination chemotherapy in addition to imatinib with DFS at 2 years of 85%.⁸ However, the limitations of imatinib in this setting were similar to those seen in CML with treatment failures and resistance to therapy viewed as significant problems.

The management of patients who are initially unresponsive to imatinib therapy or who develop resistance includes dose escalation of imatinib, switching to alternative tyrosine kinase inhibitors such as dasatinib and nilotinib, as well as hematopoietic stem cell transplantation for those who are candidates. Direct comparisons among these modalities have not been performed in a randomized fashion although there is considerable evidence demonstrating that second-generation tyrosine kinase inhibitors are effective in this setting. This article will focus on the efficacy of dasatinib in patients who are intolerant of treatment with imatinib or who have developed resistance to imatinib therapy.

Dasatinib structure and function

Dasatinib (formerly BMS-354825) is a potent inhibitor of BCR-ABL but differs from imatinib in a number of ways. Firstly, dasatinib is a 325-fold more potent inhibitor of BCR-ABL in vitro compared with imatinib and, unlike imatinib, can bind both the inactive and active conformations of the kinase molecule. As a result of dasatinib's less stringent binding requirements, it has activity against many imatinib-resistant kinase mutations.¹ In vitro cell line models revealed that dasatinib was active against 21 of 22 imatinib-resistant BCR-ABL mutations, the lone exception being the T315I mutation found within the ATP binding pocket of the ABL tyrosine kinase. The frequency of BCR-ABL mutations in patients who are resistant to imatinib ranges from

40% to 90%, with mutations more commonly found in the advanced stages of CML and in Ph+ ALL. Moreover there are more than 100 different ABL kinase point mutations reported in patients who become imatinib resistant. These mutations confer varying degrees of insensitivity to imatinib and other tyrosine kinase inhibitors.⁶

With the exception of the T315I "gatekeeper" mutation, dasatinib has shown clinical efficacy in patients with many of these mutations in the phase I and II studies described below. Patients whose CML is resistant to imatinib therapy should undergo a mutational analysis to determine if they have this, or other potentially clinically significant mutations. At this time there are no guidelines for selecting therapy based on mutational findings alone, although the presence of the T315I mutation is predictive of poor response to second-generation tyrosine kinase inhibitor (TKI) therapy.

Like imatinib, dasatinib is a multi-kinase inhibitor and inhibits other kinases such as Src family kinases (SFK) and platelet derived growth factor beta (PDGFR-B). In vitro studies evaluating the role of Src kinases in imatinib resistance have suggested a role for Src activation in non-mutated imatinib-resistant cell lines.⁹ Moreover dasatinib (unlike imatinib) is not a substrate for the P-glycoprotein efflux pump and thus may be able to achieve higher intracellular concentrations.⁷

Additionally, in contrast to imatinib, dasatinib can cross the blood brain barrier and may have clinical activity in those patients with central nervous system involvement by CML. Case reports describing responses in patients with central nervous system (CNS) leukemia utilizing dasatinib, prompted murine studies comparing imatinib and dasatinib. Dasatinib treatment resulted in a notable regression of CNS tumor growth and was associated with a dose dependent increase in survival when compared with untreated controls. Animals treated with imatinib did not experience a survival benefit and had continued tumor growth similar to untreated controls. Although dasatinib cerebrospinal fluid (CSF) concentrations in these animals were 12- to 31-fold lower than simultaneous levels in plasma, this concentration was enough to achieve 50% inhibition of CML cell lines in vitro. Low CSF concentrations of dasatinib were also observed in 15 patients with CML or Ph+ ALL. Only 6 of the 15 patients were found to have detectable levels of dasatinib in the CSF when measured 3 hours post therapy. Porkka et al. administered dasatinib to 14 other patients with imatinib-resistant CML in blast crisis or Ph+ ALL with CNS relapse.¹⁰ Eleven of the 14 patients had variable degrees of response

with complete responses in 7 patients. Of note, 5 of the 14 patients also received concomitant intrathecal chemotherapy. Three of the 14 patients experienced a CNS relapse while on dasatinib therapy and when the CSF of 2 of these patients was analyzed it was found to contain cells with point mutations within the tyrosine kinase known to be resistant to dasatinib, suggesting that dasatinib failure was due to the selection of a resistant clone.

The reason for clinical efficacy despite a modest dasatinib concentration in the CSF is unclear at this time but it has been theorized that because of dasatinib's higher potency, less drug is required to have an effect. Moreover, it is possible that the low protein environment of the CSF results in a greater unbound fraction of dasatinib. Although the study population was small, the findings are provocative and should stimulate future investigations.

Based on its multiple mechanisms of action, a number of studies evaluating dasatinib alone or in combination are underway in other tumor types, including chronic lymphocytic leukemia and lung, colon and prostate cancers.¹¹⁻¹⁶ Additionally, other studies have utilized dasatinib in patients with hyper-eosinophilic syndromes, systemic mastocytosis and multiple myeloma.¹⁷⁻¹⁹

Dasatinib is primarily metabolized by the CYP3A4 enzyme pathway and is therefore may be affected by drugs that induce or inhibit this pathway. Moreover, dasatinib's solubility is pH dependant and concomitant use of H2 blockers or proton pump inhibitors is therefore not recommended. Antacids if needed may be used 2 hours before or after dasatinib dosing.²⁰

Despite the several theoretical and mechanistic advantages of dasatinib, in vitro studies still indicate that the CML pluripotent stem cell continues to be unaffected by tyrosine kinase inhibition with dasatinib. Therefore, it is likely that

discontinuing dasatinib therapy, regardless of the prior response achieved, may result in progression of CML.²¹

Principal non-randomized studies utilizing dasatinib

Dasatinib in phase I studies

A phase I study of dasatinib in 84 imatinib refractory or intolerant patients in all phases of disease (chronic phase 40 patients, accelerated phase 11 patients and blast crisis 23 patients) as well as Ph+ ALL (10 patients) was completed in 2005.¹ Patients received dasatinib at doses of 15 to 240 mg once daily for 5 days per week. The study allowed for dosage escalations, twice-daily dosing and 7-day dosing. The rate of major hematologic response was 92% in chronic phase CML and 70% in accelerated phase, myeloid blast crisis and Ph+ ALL. Cytogenetic responses were also noted with 45% of chronic phase patients exhibiting a major cytogenetic response (35% complete). In accelerated phase, myeloid blast crisis and Ph+ ALL, major cytogenetic responses were seen in 27%, 35% and 80% of patients respectively. The duration of response was mixed and patients with myeloid or lymphoid blast crisis did poorly when compared to those in chronic phase and accelerated phase. Only 1 patient in lymphoid blast crisis and 3 patients in myeloid blast crisis had a durable response and were still in the study at a median follow up 4 months. Responses were maintained in 95% of patients with chronic phase CML and 82% of patients with accelerated phase CML with a median follow-up of 12 months and >5 months respectively.

Myelosuppression occurred in 45% and 89% of patients in chronic phase and advanced phase disease respectively. Fifteen patients had pleural effusions related to dasatinib and seven patients had transitory liver function abnormalities. Importantly, patients who discontinued imatinib due to

Table 1 Efficacy of dasatinib in phase 2 studies among imatinib-resistant patients

	N	CHR	MCyR	CCyR	Median PFS	Median OS	Median F/U
Chronic phase ²⁴	387	90%	55%	53%	NR 75% of pts w/o progression at 24 months	NR 92% alive at 24 months	24 months
Accelerated phase ²⁷	174	45%	39%	32%	NR 66% of pts w/o progression at 12 months	NR 82% alive at 12 months	14.1 months
Myeloid blast crisis ²⁹	109	26% Data from 8 months f/u ²⁸	34%	26%	6.7 months	11.8	12 months
Lymphoid blast crisis ²⁹	48	26% Data from 8 months f/u ²⁸	50%	43%	3.0 months	5.3	12 months

Abbreviations: CHR, complete hematologic response; CCyR, complete cytogenetic response; MCyR, major cytogenetic response rate; PFS, progression-free survival; OS, overall survival.

toxicity did not necessarily have recurrence of these toxicities with dasatinib. Dasatinib therapy produced hematologic and cytogenetic responses in all of the patients with BCR-ABL mutations associated with imatinib resistance with the exception of the T315I mutation.¹

Based on these findings and dasatinib's relatively short half-life (3–5 hours),²² three phase 2 studies were initiated evaluating dasatinib in chronic, accelerated and blast phases using doses of 70 mg twice a day.

Dasatinib in chronic phase

The results of a phase 2 open label international study of 387 patients with chronic phase CML who were resistant or intolerant of imatinib was published in early 2008.²³ At a median follow-up of 15.2 months, complete hematologic responses (CHR) were achieved in 90% of imatinib-resistant patients with 52% achieving a major cytogenetic response rate (MCyR). The time to CHR was rapid with the majority of patients achieving CHR within 15 days. The most common reason for discontinuation of dasatinib was toxicity (13%) followed by disease progression (7%).² In the most recent update with a minimum follow-up of 24 months, the MCyR was 55% with 88% of patients who achieved a MCyR maintaining this level of response for at least 2 years. Progression-free survival at 24 months for imatinib-resistant patients was 75%.²⁴

Thus, approximately half of patients with chronic phase CML with imatinib resistance or intolerance have significant and durable cytogenetic responses with dasatinib therapy. Further therapeutic considerations for nonresponders include alternative tyrosine kinase inhibitors and allogeneic transplantation if feasible. The optimal management of those achieving complete cytogenetic response (CCyR) is less clear. Given the relatively short follow-up, there is no guarantee that these patients will not eventually progress, and consequently the role of transplantation for these responding patients continues to be debated. Certainly these patients should be monitored closely by quantitative PCR assays for signs of relapse to avoid delays in beginning alternative measures.²⁵ For those who are not transplant candidates, however, these results are particularly encouraging and suggestive of the possibility that therapy with dasatinib may result in long-term disease control.

Dasatinib in accelerated phase

Patients with CML in accelerated phase were evaluated in another phase II open label multinational trial which included patients with imatinib resistance or intolerance.

Dasatinib was given at a dose of 70 mg twice daily until evidence of disease progression. A preliminary assessment of efficacy and safety performed on the first 107 patients with at least 8 months of follow-up was published in 2007.²⁶ The majority of patients (68%) had been treated for at least 3 years with imatinib and 59% had been treated with greater than 600 mg per day of imatinib.

In the most recent update of efficacy and safety in 174 patients with a median follow up of 14.1 months, 45% of patients achieved a CHR. Additionally, 39% of patients with imatinib resistance had a MCyR with 32% of patients achieving a CCyR. Twelve-month progression-free survival and overall survival were 66% and 82%, respectively.²⁷ Despite these encouraging results, it must be noted that the follow-up period is relatively short and that the majority of patients (61%) did not achieve a major cytogenetic response, an important predictor of long term response for de novo CML patients treated with imatinib. In addition, 19% of patients did not respond to therapy and there is no indication that the progression-free survival curves have begun to plateau suggesting that responses may be short lived.²⁶ For these reasons, allogeneic transplant should be considered for patients in accelerated phase. The search for compatible donors may be time consuming and therefore our institution begins this process when second generation TKIs are started in patients in accelerated phase.

Dasatinib in myeloid or lymphoid blast crisis

A third open label phase 2 trial evaluated patients in myeloid blast crisis (MBC) or lymphoid blast crisis (LBC) after imatinib failure or intolerance. The initial analysis with 8 months of follow up for the 74 patients in MBC and the 42 patients with LBC noted that only 43% and 12% of patients respectively, remained on study.²⁸ The median duration of therapy was 3.4 months for all patients and the most recent update with 109 and 48 patients in MBC and LBC respectively showed that major hematologic responses (MaHRs) were induced in 34% of patients with MB-CML and in 35% of LB-CML patients. MCyR were attained in 33% of patients with MB-CML and 52% of LB-CML patients, while CCyR were achieved in 26% (imatinib-resistant 26%, intolerant 20%) and 46% of patients (imatinib-resistant 43%, intolerant 67%), respectively. Median progression-free survival was 6.7 months (MB-CML) and 3.0 months (LB-CML) while median overall survival was 11.8 months and 5.3 months, respectively.²⁹

It is evident that despite advanced stages of disease, a proportion of patients do respond to dasatinib therapy. However, most of these responses are short lived and the majority of patients fail to respond. There appears to be a constant decline in the progression-free survival curves indicating that most of these patients will rapidly require additional therapies. As a consequence, patients in blast crisis should be evaluated for consideration of stem cell transplantation when therapy with dasatinib is initiated.

Dasatinib in Ph+ ALL

Murine models have suggested that tyrosine kinase activity is an important driver of leukomogenicity in Ph+ ALL.³⁰ A phase 2 study evaluating single agent dasatinib in 34 Ph+ ALL patients with imatinib resistance, resulted in 58% of patients achieving a CCyR with a minimum of 8 months of follow-up. The median progression-free survival was relatively short at 3.3 months, however. These findings clearly showed the activity of dasatinib in this population and studies utilizing dasatinib in the front-line setting as well as in combination with chemotherapy were initiated.^{31,32} In particular, the combination of Hyper-CVAD and dasatinib was evaluated in a phase 2 study of newly diagnosed or relapsed Ph+ ALL. Data from the American Society of Hematology meeting in 2007 was presented for 15 newly diagnosed and 4 relapsed Ph+ ALL patients. Dasatinib was given at a dose of 50 mg twice daily with maintenance dasatinib, vincristine and prednisone for those in complete remission. All patients with relapsed disease achieved a complete response after the first cycle with 3 of the patients achieving a CCyR. Additionally, 13 of the 14 evaluable patients with newly diagnosed ALL achieved a complete response with 1 cycle of therapy. Moreover, 10 of 11 evaluable patients achieved a CCyR.³² These results are clearly very early and may be affected by the small sample size but do indicate that dasatinib can be given in combination with chemotherapy in newly diagnosed Ph+ ALL. Further information about the duration of responses is needed and at this time most clinicians recommend allogeneic transplantation if possible when these patients achieve remission.

Toxicity and side effects of dasatinib therapy

The most common side effects of dasatinib therapy in the phase II studies were hematologic and included grade 3–4 neutropenia in 50% of chronic phase patients and 76% of accelerated phase patients. Thrombocytopenia was also common with 49% of patients in chronic phase and 82% of accelerated

phase patients having grade 3–4 thrombocytopenia.^{23,24,26,27,33} The majority of blast crisis patients developed cytopenias with 8% of patients having an episode of febrile neutropenia.^{28,29} Non hematologic toxicities included pleural effusions in 27% of patients with chronic and accelerated phase.^{23,24,26,27,33} Grade 3–4 non-malignant pleural effusions occurred in 9%, 5%, and 21% of patients in chronic phase, accelerated phase and blast crisis respectively.^{23,24,26–29,33} Pleural effusions were observed more frequently in the MB-CML cohort, with all grade pleural effusion occurring in 36% and 13% of MB and LB patients, respectively.^{28,29}

Pleural effusions appear to be a unique side effect of dasatinib and occur only rarely with imatinib or other tyrosine kinase inhibitors. The mechanism is postulated to be related to “off target” kinase inhibition. For example, CDP860, a compound engineered to block the activity of the beta-subunit of the platelet derived growth factor receptor has been shown to result in effusions when treating other tumor types³⁴ Other possibilities include interruption of vascular permeability and autoimmune mechanisms.^{35,34} Additionally, some patients developed pericardial effusions and pulmonary infiltrates. The management of pleural effusions includes close monitoring and diuresis for grade 1 (asymptomatic) effusions whereas grade 2 and 3 effusions often require thoracentesis as well as dose interruption, loop diuretics and steroids. For those with recurrent effusions, repeat drainage, shunt placement and chemical pleurodesis may be necessary if it is felt that the benefits of continued therapy outweigh the risks involved. Patients with a prior cardiac history, hypertension and those receiving twice daily therapy have an increased risk of developing this toxicity.³⁴ Patients with a history of autoimmune disease may also be at higher risk for development of effusions.³⁵ Other notable treatment-related side effects included nausea, rash, gastrointestinal bleeding, diarrhea, fatigue, headache, superficial edema and elevations of liver enzymes. The majority of these were low grade.

A less common and as yet poorly characterized phenomenon is the sudden development of lymphocytosis in patients taking dasatinib.³⁶ In vitro data have suggested that dasatinib has immunomodulatory effects on T cells and it has been suggested that this may be a result of “off target” tyrosine kinase inhibition. This phenomenon is particularly intriguing because Src kinase inhibition was theorized to induce lymphopenia and decrease thymocyte differentiation.³⁷ After a median of 3 months from the start of dasatinib therapy an abrupt lymphocytosis (peak 4–20 × 10⁹/L) was observed in 18 patients, none of whom had developed lymphocytosis while taking imatinib. These lymphocytes had morphologic

characteristics of large granular lymphocytes (LGL) and in 13 of 18 patients a proliferation of clonal cytotoxic T cells was demonstrated by immunophenotyping. The remainder of patients displayed a clonal natural killer cell phenotype. It was noted that the rate of adverse events such as pleuritis and colitis among these patients was rather high (16 of 18 patients) and clonal cytotoxic T cells were noted on biopsy specimens of some patients who developed colitis as well as in pleural effusion samples.³⁷ It was also observed that patients developing a clonal lymphocyte expansion seemed to have relatively favorable responses which included complete, long-lasting molecular responses in patients with advanced leukemia.³⁶ Indeed, we have observed this as well in one of our own patients with myeloid blast crisis who has remained in CyCR for >3 years with a T/NK lymphocytosis. The incidence of lymphocytosis and whether it is indeed associated with “inflammatory” type toxicities and improved response in patients, presumably by immune mediated mechanisms, needs to be evaluated in larger groups of patients and hopefully such analyses of the large number of patients on the dasatinib trials will be forthcoming shortly.

Dose optimization with dasatinib

The three phase 3 studies evaluating dasatinib utilized a dose of 70 mg bid based on its relatively short half-life (3–5 hours) and earlier pharmacokinetic and pharmacodynamic studies. However, in the phase 1 study, hematologic and cytogenetic responses were also noted with once-a-day dosing. Moreover, as a result of dose reductions, the median daily dose of dasatinib in the phase I study was 101 mg.^{1,38} Longer-term follow-up also suggested that pleural effusions were less common with once-daily dosing.³⁸ Consequently, a phase III randomized trial evaluating different doses and schedules of dasatinib in patients with imatinib-intolerant or -resistant chronic phase CML was conducted.³⁸ Seven hundred and twenty-four patients were randomized to receive 100 mg daily, 140 mg daily, 50 mg twice daily or 70 mg twice daily. Dose escalations and reductions were allowed for inadequate response and toxicity. With a minimum follow-up of 6 months and a median duration of therapy of 8 months, there was no difference in the rates of CHR, MCyR, progression-free survival, overall survival or disease progression among the four arms.

The rates of key treatment-related adverse events (ie, cytopenias and pleural effusions) were consistently lower in patients receiving dasatinib 100 mg once daily than for the other treatment groups. Overall, significantly fewer patients treated with the 100 mg once daily dose experienced

grade 3–4 adverse events when compared to patients receiving the currently approved 70-mg twice-daily dose (30% vs 48%; $p < 0.001$). In particular, grade 3/4 thrombocytopenia was decreased (22% vs 37%; $p < 0.004$). The currently approved dosing schedule of 70 mg twice daily had significantly higher rates of pleural effusion (any grade) compared with the 100 mg once-daily arm (16% vs 7% $p = 0.024$) as well as higher incidences of nausea (25% vs 15%) and vomiting (10% vs 5%). As a result, fewer patients in the 100 mg daily-dose arm had dosage reductions (22% vs 32%) or interruptions (27% vs 35%) compared with the 70 mg twice-daily arm. Additionally, discontinuation owing to toxicity occurred in only 4% of patients treated with 100 mg once daily as compared with 11% of patients treated with 70 mg twice daily.

These results indicated that the 100 mg daily dosing regimen offered the best risk/benefit ratio of the doses compared. Although the follow-up is relatively short, these findings are consistent with the early results of the phase 2 studies investigating dasatinib. It should be noted that these results are for patients in chronic phase and that higher doses may be necessary to achieve adequate responses in more advanced disease. The current recommended starting dose continues to be 70 mg twice a day in patients with accelerated and blast crisis CML. A similarly designed dose optimization study in accelerated and blast phase CML is underway and has completed accrual.³⁹

Principal clinical studies comparing dasatinib with other therapies

Dasatinib versus other TKIs

Prior to the availability of second-generation TKIs, the most commonly utilized therapy for imatinib-resistant CML patients was dose escalation. A phase 2 study evaluated the relative benefit of 70 mg of dasatinib twice daily versus a dose escalation to 800 mg of imatinib.⁴⁰ One hundred and fifty patients with chronic phase CML whose disease had progressed on 400 to 600 mg/day of imatinib were randomized in a 2:1 ratio to dasatinib or dose-escalated imatinib. Patients with mutations known to have a high resistance to imatinib were excluded and crossover was allowed if there was confirmed progression, lack of MCyR at 12 weeks, or intolerance despite dose reduction. More than two-thirds of patients had received treatment with 600 mg of imatinib. With a median follow-up of 15 months, CHR and CCyR were found to be significantly more common in the dasatinib arm (Table 2). Major molecular responses were also more frequent with dasatinib (16% vs 4%, $p = 0.038$).

Table 2 Dasatinib versus 800 mg imatinib: all patients⁴⁰

	N	CHR%	MCyR	CcyR	Post crossover response	Median time to treatment failure	Median follow up
Dasatinib	100	93	52%	40%	45%	NR	15 months
Imatinib 800 mg	50	82	33%	16%	15%	3.5 months (CI, 3.3–3.8 months)	15 months
p value		0.034	0.023	0.004	0.063		

Abbreviations: CHR, complete hematologic response; CCyR, complete cytogenetic response; MCyR, major cytogenetic response rate.

Patients with the highest pre-study likelihood of imatinib resistance, namely those unable to achieve a MCyR on imatinib and those progressing on 600 mg of imatinib daily, had significantly higher rates of MCyR with dasatinib use. However, the rates of MCyR in those who receiving 400 mg of imatinib daily prior to enrollment were similar for the dose escalation or dasatinib population (53% vs 58%) (Table 3). The median time to treatment failure and response after crossover favored the dasatinib arm. The most common reason for imatinib discontinuation was disease progression (61%) whereas discontinuation of dasatinib was most often due to intolerance (16%). Progression-free survival showed an 86% relative risk reduction in favor of dasatinib.

Grade 3–4 non-hematologic toxicity was minimal for both treatment groups. All-grade superficial edema (15% vs 43%) and fluid retention (30% vs 45%) were less common with dasatinib than imatinib, whereas pleural effusion (17% vs 0%; grade 3–4, 4% vs 0%) was more common. Cytopenias, particularly thrombocytopenia, was more profound in the dasatinib group. These data suggest that in those patients who are unable to achieve MCyR with imatinib or in those patients failing to respond to 600 mg of imatinib daily, the preferred second-line therapy is a second-generation TKI. In patients who do not respond to 400 mg of imatinib daily or in those who progress at this dose, both dose escalation or switching to a second-generation TKI remain reasonable alternatives.

Dasatinib versus hematopoietic stem cell transplantation

A retrospective analysis of 420 patients who failed imatinib therapy was performed with the goal of evaluating the most promising second-line therapy.⁴¹ Outcomes were grouped by the patient's phase of disease at the time of relapse. Eighty-eight patients had progressed on imatinib but remained in chronic phase. The outcomes of these patients were the most encouraging, with 3-year survival rates of

72% regardless of the type of second-line therapy chosen. Patients who were in accelerated phase at the time of progression or progressed to accelerated phase from chronic phase while on imatinib therapy, had a 3-year survival of only 30%, whereas patients progressing to blast crisis or remaining in blast crisis with imatinib resistance performed poorly with 3-year survival rates of only 7%.

Patients who remained in chronic phase at the time of progression appeared to do better with second generation TKIs rather than allogeneic stem cell transplant. In a multivariable analysis however, second-line therapy was not identified as an independent prognostic factor for survival possibly due to the limited follow-up and the multiple, poorly characterized reasons why some patients were referred for transplantation and others not. This retrospective analysis in combination with the results of the dasatinib study in chronic phase mentioned earlier lends support to the notion that some patients in chronic phase may do well with dasatinib therapy alone. Additionally, this study supports the inferences from the phase 2 studies that patients with more advanced disease have relatively poor outcomes with dasatinib alone and that stem cell transplantation should be considered. However, this study does not provide insight into whether patients who respond to dasatinib benefit from transplantation as compared to continued treatment with dasatinib.

Other alternatives to dasatinib Nilotinib

Nilotinib (formerly AMN107) is an orally active aminopyrimidine- derivative tyrosine kinase inhibitor with 20 to 50 times the inhibitory activity of imatinib in imatinib sensitive cell lines. Like imatinib, nilotinib binds only the active conformation of the kinase molecule and functions through competitive inhibition at the ATP binding site. Nilotinib has been shown to be active against 32 of 33 mutations found in the BCR-ABL kinase domain.⁴² The only mutation found to be unaffected by nilotinib usage is, as in the case

Table 3 Response to dasatinib stratified by prior therapy and response⁴⁰

	All patients	Failed to achieve MCyR to imatinib	Prior imatinib dose \geq 600 mg	Prior imatinib dose = 400 mg
Dasatinib	N = 101	N = 39	N = 63	N = 38
MCyR	52%	49%	49%	58%
Imatinib	N = 49	N = 15	N = 34	N = 14
MCyR	33%	7%	24%	53%
p value	0.023	0.006	0.015	NS

Abbreviation: MCyR, major cytogenetic response rate.

of dasatinib, the T315I mutation. Based on phase 1 studies, a dose of 400 mg twice daily was thought to be optimal for phase 2 evaluation.

In the most recent update of a phase 2 trial of nilotinib in 320 patients with imatinib failure in chronic phase who had received nilotinib for at least 6 months, the CHR rate, MCyR rate and CCyR rate were 76%, 56% and 40% respectively.⁴³ Nilotinib was also evaluated in 119 patients in accelerated phase CML. With all patients receiving at least 6 months of therapy, only 26% of patients achieved a CHR. MCyR and CCyR were noted in 29.4% and 16% of patients respectively.⁴⁴ One hundred thirty-five imatinib-resistant patients with blast crisis were also evaluated in a phase II study and found to have a CHR in 24% of patients with MBC and 28% of patients with LBC. However, it was noted that 88% of patients discontinued therapy at a median of 84 days largely due to disease progression.⁴⁵ Cytopenias were the most common toxicity⁴³⁻⁴⁵ and non-hematologic side effects included liver function abnormalities (predominantly asymptomatic unconjugated hyperbilirubinemia), rash as well as asymptomatic lipase elevations in ~15% patients.⁴²⁻⁴⁵ QT prolongation noted in the phase 1 study was not an issue in the follow up phase 2 populations.⁷

None of these studies utilized an additional control or experimental arm and inferences about the efficacy of nilotinib comparison with dasatinib are speculative, although the response rates seem to be in the same range. Therefore, unless a randomized study is performed (an unlikely prospect), no data support the preferential use of either TKI for patients with imatinib-resistant CML. An exception may be for certain mutations which have better in vitro sensitivity to one agent or another such as P-loop and F359I/V mutations, which are more sensitive to dasatinib, and F317L mutations which are more sensitive to nilotinib.⁴⁶ Additionally, drug selection should also be based on side-effect profile. For example, for patients in whom there might be increased concern about fluid retention, nilotinib may be the more suitable choice, whereas for patients with a history of pancreatitis, dasatinib might be preferred.

Emerging therapies

There are a number of emerging therapies which may improve on the current treatments for CML. They can be organized into 3 broad categories. The first is the use of tyrosine kinase inhibitors in combination with other therapies to improve remission rates and discourage the development of resistance. Combination therapy may result in inhibition of critical downstream events responsible for imatinib resistance. For instance, it has been shown that the PI3K/Akt pathway is important in this process and the serine/threonine protein kinase mTOR is a downstream component of this pathway. In BCR-ABL positive cells the mTOR pathway is constitutively active, resulting in phosphorylation of its substrates. Inhibition of this mechanism with rapamycin, an mTOR inhibitor has shown activity against imatinib-resistant cell lines.⁴⁷ Combination therapy with mTOR inhibitors and imatinib may result in fewer frontline failures and therapy may be well tolerated.

A second possibility is the development of additional BCR-ABL inhibitory TKIs with different kinase inhibition profiles compared to imatinib and second generation TKIs. Examples include bosutinib, which inhibits Src family kinases but not KIT or PDGFR, and INNO-406 which inhibits ARG and FYN kinases.⁷ As newer drugs are identified for refractory disease, they are also being tested in previously untreated patients as well. Studies comparing dasatinib, nilotinib and bosutinib to imatinib in newly diagnosed chronic phase CML are underway.^{48-50,54} If durable cytogenetic response rates are significantly improved with the use of these medications in the front line setting, it is possible that a smaller percentage of patients will ultimately develop treatment resistance.

Lastly, new small molecule non-ATP-competitive inhibitors designed to address the T315I mutation are under development.⁶ In vitro results are intriguing and phase 1 trials are being initiated.

Conclusions

Therapy with imatinib has revolutionized the treatment of CML although “only” ~65% of chronic phase patients remain

in CCyR on imatinib after 5 years of treatment, leaving some room for improvement.⁴ Dasatinib has emerged as an effective second-line therapy for many of these imatinib-resistant patients. However, ~50% of imatinib-resistant chronic phase patients do not have cytogenetic responses with dasatinib treatment and the responses in more advanced stages are generally not durable. Thus, hematopoietic stem cell transplantation must be considered in non-responders to dasatinib and in those in more advanced stages. Additionally, despite the several theoretical and mechanistic advantages of dasatinib, *in vitro* studies still indicate that the CML stem cell continues to be unaffected by tyrosine kinase inhibition with dasatinib. Therefore, it can be theorized that discontinuing therapy, regardless of the response achieved, may result in progression of CML.²¹

The role of second-generation TKIs in newly diagnosed patients is currently being evaluated. Preliminary results are promising for both drugs. Nilotinib and dasatinib were evaluated in patients with untreated chronic phase CML and produced favorable early results compared with historical data with imatinib. Ninety-five percent of 32 patients achieved CCyR after 3 months of therapy with nilotinib.⁵¹ Dasatinib was evaluated in 37 patients and at 3 months, 79% of patients have achieved a CCyR.⁵² These results along with the efficacy of these agents in the second-line setting have provided the impetus for the randomized phase 3 studies mentioned above.^{53,55}

Disclosures

The authors have no conflicts of interest to disclose.

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