Dasatinib in the first-line treatment of chronic myeloid leukemia

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Dasatinib has been approved for first-line treatment of chronic-phase chronic myeloid leukemia by the Food and Drug Administration and is recommended as a first-line treatment option by the National Comprehensive Cancer Network. Based on in vitro data, dasatinib seems to be less susceptible to the resistance mechanisms that affect imatinib. Dasatinib is an effective second-line treatment in patients who are resistant to imatinib. First-line clinical data show that dasatinib provides more rapid and deeper degrees of response than does imatinib, which may correlate with improvements in long-term patient outcome. Grade 1 or 2 cytopenias are the most common adverse events of first-line dasatinib treatment. In a phase 3 comparison with imatinib, several types of nonhematologic adverse events were less frequent in the dasatinib arm; frequencies of grade 3 and 4 events were ≤ 2%. Among patients with a minimum follow-up of 24 months, grade 1 or 2 pleural effusion was reported in 14% of dasatinib-treated patients and was manageable in almost all cases; no grade 3 or 4 pleural effusion occurred. Prompt and effective monitoring and management of dasatinib toxicities is essential to minimize intolerance and nonadherence to therapy. Patient education is important to increase the likelihood of prompt management and provide reassurance. Recommendations for patient monitoring, management, and education are provided.

Chronic myeloid leukemia (CML) was responsible for 11.3% of new leukemia cases in 2010.[1] Between 2004 and 2008, the incidence of CML per year was 1.6 cases per 100,000 population, and the median age at diagnosis was 65 years.[2] Classically, CML has a tripartite clinical course. If it is left untreated, it progresses from a relatively benign chronic phase (CP) to a fatal blastic phase (BP), normally through an accelerated phase (AP).[3,4] Patients typically present with symptoms of fatigue, weight loss, and anorexia, and nearly half of all patients show signs of splenomegaly.[4] However, about 40% of patients with CML are asymptomatic at presentation and are diagnosed after routine blood testing for unrelated reasons.[4]

The pathophysiology of CML is caused by the BCR-ABL gene fusion, a constitutively active oncogenic tyrosine kinase that is usually associated with the Philadelphia chromosome, a reciprocal translocation between chromosomes 9 and 22.[5] BCR-ABL inhibitors are the mainstay of CML treatment although stem-cell transplantation may be considered for advanced-phase patients despite the substantial associated mortality and late morbidity.[6] Imatinib was the first BCR-ABL inhibitor introduced for the treatment of CML. The Food and Drug Administration (FDA) approved it in 2001 for the treatment of interferon-resistant or -intolerant CML and as a first-line therapy in 2002.[7,8] In a phase 3 trial (the International Randomized Study of Interferon versus STI571 [IRIS]) in 1,106 patients with untreated CML-CP, the rate of complete cytogenetic response (CCyR) at 18 months with imatinib 400 mg per day was just over 5 times higher than it was with interferon-α plus low-dose cytarabine (76% vs 15%, respectively; $P < .001$).[9] However, long-term follow-up has demonstrated that many patients develop clinical resistance to imatinib, which often requires a change in treatment. In a large, single-institution study of imatinib in 204 patients who were analyzed by intent-to-treat, 26% of patients with CML-CP discontinued imatinib because of adverse events, disease progression, loss of response, or failure to achieve a major cytogenetic response (MCyR) after a median follow-up of 38 months.[10] The best characterized mechanism of imatinib resistance is the acquisition of drug-resistant BCR-ABL mutations, more than 100 of which have been reported in patients who are resistant to imatinib.[11] Other mechanisms potentially associated with resistance include dysfunctional activation of SRC family kinases, altered expression of drug influx and efflux proteins (including organic cation transporter-1), the acquisition of additional

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chromosomal abnormalities outside of BCR-ABL, and overexpression of BCR-ABL.[12-15] Consequently, additional first-line treatment options are needed.

Dasatinib is a second-generation oral BCR-ABL inhibitor that was initially approved for treating CML after failure of or intolerance to first-line therapy, including imatinib.[16] It was approved for the first-line treatment of patients with CML-CP based on findings from a phase 3 randomized trial (Dasatinib versus Imatinib Study in Treatment-Naïve CML Patients [DASISION]).[17] The recommended starting doses are 100 mg once daily for patients with CML-CP and 140 mg once daily for those with advanced disease (CML-AP or -BP).[16]

Nilotinib, another second-generation BCR-ABL inhibitor, was initially approved for the treatment of patients with CML-CP or CML-AP that was resistant or intolerant to first-line treatment, including imatinib, at a dosage of 400 mg twice daily.[18] Nilotinib also has been approved in the first-line setting for CML-CP based on the results of a recent phase 3 study in patients with newly diagnosed CML,[19] with a recommended dosage of 300 mg twice daily.[18] This article reviews the rationale for dasatinib as first-line treatment in CML-CP, including clinical experience and the monitoring and management of toxicity in this setting.

The rationale for dasatinib as first-line treatment

The activity and tolerability of second-line dasatinib in patients with prior imatinib therapy across all phases of CML were established in the SRC/ABL Tyrosine kinase inhibition Activity Research Trials of dasatinib (START) phase 2 studies. After 2 years' follow-up in the START-C study of patients with CML-CP who were resistant or intolerant to imatinib, CCyR and major molecular response (MMR) rates to dasatinib 70 mg twice daily were 53% and 47%, respectively, and the overall survival rate was 94%.[20] Induced responses were durable; 90% of patients who achieved a CCyR maintained their response 24 months later.[21] The recommended starting dose for dasatinib, 100 mg once daily in patients with CML-CP,[16] is based on a phase 3 dose-optimization study of 670 patients that showed that dasatinib 100 mg once daily had a similar efficacy to other schedules (50 mg twice daily, 140 mg once daily, and 70 mg twice daily), but with reduced toxicity.[22] After a minimum of 2 years' follow-up in the 100-mg, once-daily arm (n = 167), CCyR and 24-month overall survival rates were 50% and 91%, respectively.[22] Rates of all-grade pleural effusion, grade 3 or worse thrombocytopenia, all-grade neutropenia, and all-grade leukopenia were significantly lower in the 100-mg, once-daily arm compared with other schedules.[23]

Dasatinib is thought to be effective in patients who are resistant to imatinib because it is less susceptible to certain resistance mechanisms that affect imatinib. Dasatinib is 325-fold more potent in inhibiting BCR-ABL than is imatinib, which allows it to counter the resistance mediated by BCR-ABL overexpression.[24] Unlike imatinib, dasatinib binds to the active conformation of BCR-ABL[25,26] which may allow dasatinib to bind more effectively to some imatinib-resistant BCR-ABL mutations.[25] Dasatinib is also a potent inhibitor of SRC family kinases activity.[27]

In a retrospective study of patients with imatinib-resistant disease in the START-C, START-R, and dose-optimization trials, dasatinib was associated with higher rates of CCyR (72% vs 42%, respectively) and 24-month event-free survival (89% vs 29%) if administered after loss of only MCyR during imatinib treatment compared with loss of MCyR and complete hematologic response (CHR).[28] In a separate study, shorter time from CML diagnosis to dasatinib treatment, younger age, and lower percentage of Philadelphia chromosome–positive cells were found to be favorable predictive indicators for long-term cytogenetic response.[29] Taken together, this suggests that earlier treatment with dasatinib may be clinically advantageous.

Efficacy in the first-line setting

The first study of dasatinib as first-line therapy was a phase 2 open-label study in which 62 patients with early CML-CP were randomized to dasatinib 50 mg twice daily (31 patients) or 100 mg once daily (31 patients).[30] Among the patients who were eligible for cytogenetic and molecular response assessment (treated for at least 3 months; 50 patients), 98% had achieved a CCyR at any time on study; the median time to CCyR was 3 months (Table 1).[30] These data compare favorably with historic data for imatinib from the same institution.[31] Molecular responses were deep and rapid, including an overall MMR rate of 82% and a median time to MMR of 6 months.[30] Of note was that the responses proved to be durable; all of the patients were alive at data cut-off (median follow-up time of 24 months), and none progressed to advanced disease. No significant differences were seen between treatment schedules for efficacy or safety.[30] However, because of the significantly improved safety profile for the 100-mg once-daily schedule compared with other schedules in the second-line setting,[22,23] accrual will only continue for the dasatinib 100-mg, once-daily schedule.

A trial is ongoing to compare the efficacy of dasatinib and imatinib in the first-line setting.[17,32] DASISION is an open-label, multinational, randomized phase 3 trial. In all, 519 patients with newly diagnosed CML-CP were randomized to receive dasatinib 100 mg once daily (259

TABLE 1 Efficacy of first-line dasatinib in chronic-phase chronic myeloid leukemia

Study (no. of patients)	Dasatinib dosage	Follow-up, mo	Response rates, %				Survival rates, at 24 mo %		
			CHR	MCyR	CCyR	MMR	PFSs[a]	EFS[b]	OS
MD Anderson Cancer Center[30] (50)	100 mg QD or 50 mg BID	24 (median)	100	98	98	82	n/a	88	100
DASISION[32] (258)	100 mg QD	24 (minimum)	n/a	n/a	86[c]	64	93.7	n/a	95.3

Abbreviations: BID, twice daily; CCyR, complete cytogenetic response; CHR, complete hematologic response; EFS, event-free survival; MCyR, major cytogenetic response; MMR, major molecular response; mo, months(s); n/a, not available; no., number; OS, overall survival; PFS, progression-free survival; QD, once daily.

[a] Progression was defined as doubling of white blood cell count to $>20 \times 10^9$/L in the absence of CHR, loss of CHR, increase in Philadelphia chromosome-positive metaphases to >35%, development of accelerated phase or blast phase, or death from any cause; [b] Events were defined as loss of CHR or CCyR, therapy discontinuation for toxicity or lack of efficacy, development of accelerated phase or blast phase, or death from any cause; [c] Rate of confirmed response (on 2 consecutive occasion's ≥28 days apart) by 12 months (primary end point) was 80%.

patients) or imatinib 400 mg once daily (260 patients). The 24-month cumulative rate of confirmed CCyR (the primary end point) was 80% and 74%, respectively; and CCyR (measured using the standard definition) was 86% and 82% (Table 1).[32] After 12 months of follow-up, rates of CCyR by 3, 6, and 9 months showed a similar trend (54%, 73%, and 78% for dasatinib vs 31%, 59%, and 67% for imatinib).[17] The 24-month cumulative rate of MMR was 64% for dasatinib, compared with 46% for imatinib.[32] The median time to MMR was 15 months, compared with 36 months. After 12 months of follow-up, the rates of MMR by 3, 6, and 9 months showed a similar trend (8%, 27%, and 39% for dasatinib vs 0.4%, 8%, and 18% for imatinib).[17] The cumulative CCyR and MMR rates across the period analyzed were higher for dasatinib compared with imatinib ($P = .0002$ and $P < .0001$, respectively).[32] Dasatinib provides more rapid responses and deeper degrees of response than imatinib, which may correlate with improvements in long-term patient outcome, as early molecular responses are associated with increased probability of MCyR, more durable CCyRs, and less risk of later loss of MMR or emergence of BCR-ABL mutations.[33-40]

Monitoring first-line treatment

Recommendations and guidelines for the treatment and monitoring of CML have been set out by the European LeukemiaNet (ELN)[6,41] and the National Comprehensive Cancer Network (NCCN).[42] Both sets of guidelines contain proposals on when to change to second-line treatment according to hematologic or cytogenetic response after treatment initiation.[41,42] If patients who receive first-line imatinib do not achieve an optimal response (defined as CHR at 3 months [also with at least minor cytogenetic response according to ELN], at least partial cytogenetic response at 6 months, and CCyR at 12 months), switching to dasatinib or nilotinib can be considered or is recommended, depending on level of response achieved. For patients who progress to AP or BP or who have a T315I mutation, hematopoietic stem-cell transplantation is recommended.[6] NCCN guidelines have been updated recently to include the use of dasatinib and nilotinib as first-line options for CML-CP.[42]

The ELN and NCCN recommendations for switching treatment are based on hematologic and cytogenetic responses, the surrogate end points of clinical outcomes. As in other diseases, surrogate end points in CML are often used to reduce the length of a study, thereby accelerating the timeline for obtaining regulatory approval from the regulatory authorities.[43] Surrogate end points are also useful for predicting long-term outcomes based on short-term treatment responses. Most of the current understanding of surrogate end points in CML originates from results based on landmark analyses estimating long-term survival outcomes in patients with specified levels of response at a given time point. For example, data from IRIS have demonstrated survival advantages for key molecular and cytogenetic markers in landmark analyses, including CCyR at 12 months,[44] MMR at 12 months,[38] CCyR at 18 months,[45] MMR at 18 months,[38] and CCyR + MMR at 18 months.[44] More recently, studies in imatinib- and dasatinib-treated patients in the first-line setting have reported that the achievement a BCR-ABL level at ≤ 10% at 3 months correlates with better long-term outcomes and a lower risk of disease progression than does the achievement of a BCR-ABL level of > 10% at 3 months.[46-49] These data suggest that the BCR-ABL level at 3 months is an important surrogate end point in CML. Although surrogate end points can be useful for predicting long-term outcomes based on short-term responses, they are also limiting in that they are correlates of rather than direct measures of established clinical end points.[43]

TABLE 2 Drug-related adverse events occurring in ≥10% of treated patients in DASISION

Toxicities	Dasatinib (n = 258)		Imatinib (n = 258)	
	All grades, %	Grade 3 or 4, %	All grades, %	Grade 3 or 4, %
Hematologic events				
Neutropenia	65[a]	24	58[a]	21
Thrombocytopenia	70[a]	19	62[a]	11
Anemia	90[a]	11	84[a]	8
Nonhematologic events				
Fluid retention	25	2	43	2
Superficial edema	11	0	36	<1
Pleural effusion	14	1	0	0
Diarrhea	19	<1	21	1
Nausea	10	0	23	0
Vomiting	5	0	10	0
Myalgia[b]	22	0	39	0
Rash	11	0	17	1
Headache	13	0	11	0
Fatigue	9	<1	11	0
Hypophosphatemia	–	7		25

Adapted from Kantarjian et al.[17,32] with permission.
[a] Haematologic events (all grades) were only reported for 12 month follow up[17]; [b] Includes myalgia, muscle inflammation, and musculoskeletal pain.

Safety of first-line treatment

In DASISION, most drug-related adverse events were grade 1 or 2 for dasatinib and imatinib and the most frequent grade 3 or 4 adverse events were hematologic events (Table 2),[32] similar to previous observations across all approved BCR-ABL inhibitors.[8,16,18] The incidence of grade 3 or 4 neutropenia and anemia was similar in both arms; grade 3 or 4 thrombocytopenia was more frequent with dasatinib.[32] Among all-grade nonhematologic adverse events that occurred in at least 10% of either arm, most adverse events occurred less frequently for patients receiving dasatinib or at a frequency similar to that for patients receiving imatinib. Adverse events occurring less frequently with dasatinib included nausea, vomiting, myalgia, rash, and fluid retention, including superficial edema (Table 2). In contrast, pleural effusion was seen with dasatinib but not imatinib. After a minimum follow-up of 24 months, 2 cases of grade 3 or 4 pleural effusion were reported; grade 1 or 2 pleural effusion was reported in 14% of patients, but led to few treatment discontinuations (5 of 258 patients). Pleural effusion did not seem to affect efficacy, as shown by the CCyR rate of 92% by 12 months in patients with pleural effusion.[17] Dasatinib may also increase the risk of pulmonary arterial hypertension (PAH) at any time following treatment initiation including after more than a year of therapy.[16] All-grade bleeding events were reported in 5% of patients in both arms after 12 months of follow-up;[17] the incidence of grade 3 or 4 bleeding was 1% in both arms after 24 months of follow-up.[32] A QTc interval between 450 and 500 msec occurred in 2% of the dasatinib arm and in 4% of the imatinib arm; a QTc interval of longer than 500 msec was rare (< 1% of patients).[17] Grade 3 and 4 hypophosphatemia was more frequent in the imatinib arm (25% vs 7%, respectively).[32]

Management of adverse events

Monitoring and managing toxicities promptly and effectively as they arise during treatment with any BCR-ABL inhibitor is paramount. The development of intolerance or a decrease in the level of treatment adherence must be avoided as much as possible. Intolerance may be defined broadly as treatment discontinuation due to toxicity despite the potential for further efficacy with ongoing treatment. During the first 24 months of treatment with first-line dasatinib in the DASISION trial, 7% of patients discontinued therapy for drug-related toxicity.[32] Poorly managed toxicities also may lower patient adherence, which in turn may reduce the efficacy of dasatinib treatment. Recent prospective studies in patients with CML receiving imatinib showed that reduced adherence was associated with significantly worse responses.[50] In partic-

TABLE 3 Dose-modification guidelines for management of dasatinib adverse events in the first-line setting in patients with chronic-phase chronic myeloid leukemia

Adverse event	Guidelines
Hematologic	If ANC $< 0.5 \times 10^9$/L or platelets $< 50 \times 10^9$/L, interrupt therapy until ANC $\geq 1.0 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L, then resume treatment at previous dose if recovery occurs in ≤7 days. If platelets $< 25 \times 10^9$/L or ANC $< 0.5 \times 10^9$/L recurring for > 7 days, repeat initial step then resume treatment at 80 mg once daily for second episode or 50 mg once daily for third episode (for newly diagnosed patients) or discontinue treatment (for patients resistant or intolerant to prior therapy including imatinib).
Nonhematologic	If a severe event occurs, interrupt therapy until resolved or improved, then resume therapy at reduced dose depending on the initial severity of event.

Abbreviation: ANC, absolute neutrophil count.
Based on information from Sprycel (dasatinib) PI, 2010.[16]

ular, one study found that patients with one of several adverse events (asthenia, nausea, muscle cramps, and bone or joint pains) had lower rates of adherence to imatinib.[51]

Hematologic adverse events can be managed through dose interruption or reduction (Table 3). Growth factor support also may be indicated.[42] Nonhematologic adverse events, such as pleural effusion, are managed by dose interruption and reduction (Table 3).[17,42,52-56] Diuretics and steroids also may be useful for managing fluid-retention events.[16,42,53-55] Rare cases of severe pleural effusion may require thoracentesis and oxygen therapy.[16,54,55] PAH may be reversible upon treatment discontinuation; upon a confirmed PAH diagnosis, dasatinib should be permanently discontinued.[16] For bleeding events, management steps include dose interruption and transfusion.[16,57] Rash may be managed with topical or systemic steroids in addition to dose reduction, interruption, or discontinuation.[42] In cases of gastrointestinal upset, it has been suggested that dasatinib should be taken with a meal and a large glass of water. Specific supportive medication is indicated in case of diarrhea.[42]

Monitoring and patient education

Prior to administration of dasatinib, hypokalemia, and hypomagnesemia must be corrected. Patients should also be assessed for signs or symptoms consistent with cardiac dysfunction prior to and during dasatinib treatment and treated accordingly.[16] QT prolongation is a rare, but potentially very serious event. Dasatinib should be administered with caution to patients who have or may develop QT prolongation, such as those with congenital long QT syndrome or those taking drugs that may lengthen the QT interval and those who have received cumulative anthracycline therapy. To assess patients for hematologic toxicities, blood counts should be monitored weekly for the first 2 months of treatment and then monthly or as clinically indicated.[16] Due to a risk of bleeding, dasatinib also should be used with caution in patients receiving anticoagulant drugs or drugs that inhibit platelet function, and such patients should be monitored accordingly. Most bleeding events are associated with severe thrombocytopenia. Patients exhibiting symptoms of pleural effusion should be evaluated by chest radiograph.[16] In analyses of patients who received dasatinib after prior imatinib, independent risk factors for pleural effusion that were identified included use of a twice-daily schedule, a history of cardiac disease or hypertension, hypercholesterolemia, autoimmune disease, or rash on prior imatinib.[55,58] In a recent analysis of patients with CML-CP receiving the recommended starting dose of 100-mg, once-daily dasatinib, only advanced age and development of lymphocytosis were identified as risk factors for pleural effusion, but data on comorbidities were not collected uniformly and therefore were excluded from the risk factor analysis.[59]

Patients need to be educated about potential adverse events of dasatinib therapy. This education increases the likelihood of prompt intervention and re-assures the patient that such toxicities are common and may be managed. Patients should be educated to recognize and report symptoms of key toxicities, including increased shortness of breath, fever, unusual bleeding or bruising, swelling or weight gain, diarrhea, headache, nausea, vomiting, musculoskeletal pain, significant fatigue, or significant skin rash.[16] Female patients of childbearing potential should be counseled to avoid pregnancy.[16]

At each visit, concomitant medications should be reviewed. The patient should report all other medications being taken, including over-the-counter supplements. Dasatinib is metabolized primarily by hepatic CYP3A4 enzymes; therefore inducers of this enzyme may decrease dasatinib exposure, and inhibitors may increase exposure.[16] If a potent CYP3A4 inhibitor must be administered concomitantly with dasatinib, a dasatinib dose de-

TABLE 4 Drug interactions with dasatinib

Drug effect	Drug name
Drugs that may increase dasatinib plasma concentrations	CYP3A4 inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole)
Drugs that may decrease dasatinib plasma concentrations	CYP3A4 inducers (eg, carbamazepine, dexamethasone, phenobarbital, phenytoin, rifabutin, rifampin, St John's wort), histamine-2 antagonists (eg, cimetidine, famotidine, ranitidine), proton pump inhibitors (eg, esomeprazole, lansoprazole, omeprazole, pantoprazole sodium, rabeprazole), antacids (eg, aluminum hydroxide, magnesium hydroxide, calcium carbonate)
Drugs that may have their plasma concentration increased by dasatinib	CYP3A4 substrates (eg, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine)

Based on information from Sprycel (dasatinib) PI, 2010.[16]

crease to 20 mg daily should be considered in patients with CML-CP. Any subsequent toxicities should be monitored carefully, and treatment with dasatinib or the CYP3A4 inhibitor may have to be interrupted. Grapefruit juice also should be avoided. Conversely, if a potent CYP3A4 inducer must be taken with dasatinib, a dasatinib dose increase should be considered. In addition, dasatinib may inhibit the metabolism of other drugs that are substrates of CYP3A4. Caution must therefore be taken with such drugs that have a narrow therapeutic index (Table 4). Because the solubility of dasatinib is pH dependent, antacids must be taken 2 hours before or after dasatinib administration. However, antacids should be taken in preference to gastric acid suppressants, such as histamine-2 blockers or proton pump inhibitors, which may reduce dasatinib exposure.[16]

Conclusions

Long-term follow-up has demonstrated that clinical resistance to imatinib develops in many patients, requiring a change in treatment. Dasatinib, a compound less sensitive to major mechanisms of imatinib resistance, is effective in treating patients resistant to imatinib. New data demonstrate an increased clinical benefit associated with using dasatinib earlier in the treatment algorithm. In the first-line setting, dasatinib 100 mg once daily has greater efficacy than imatinib 400 mg once daily. Clinically significant adverse events, including pleural effusion, generally are manageable. The toxicity-related discontinuation rate compares favorably with that of imatinib in the same setting. Dasatinib is now approved by the FDA for the first-line treatment of CML-CP, and recently updated NCCN guidelines include the use of dasatinib in this setting. The NCCN and ELN guidelines offer the most current guidance for selecting treatment based on monitoring treatment response at key time points.[5]

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