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CASE REPORT

Efficacy and Tolerability after Unusually Low Doses of Dasatinib in Chronic Myeloid Leukemia Patients Intolerant to Standard-Dose Dasatinib Therapy

Mariana Serpa[1,2], Sabri S. Sanabani[3,4], Israel Bendit[1], Fernanda Seguro[1,2], Flávia Xavier[1,2], Cláudia Bitti Barroso[2], Monika Conchon[1] and Pedro Enrique Dorlhiac-Llacer[1]

[1]Department of Hematology, Faculty of Medicine, University of São Paulo, São Paulo, Brazil. [2]Cancer Institute of São Paulo, Brazil. [3]Clinical Immunology and Allergy Division, University of São Paulo, São Paulo, Brazil. [4]Department of Translational Medicine, Federal University of São Paulo, São Paulo, Brazil. Corresponding author email: marianaserpa@hotmail.com

Abstract: We report our experience in 4 patients with chronic myeloid leukemia (CML) who had discontinued imatinib as a result of adverse events and had switched to dasatinib. The chronic phase (*n* 2) and accelerated phase (*n* 2) CML patients received dasatinib at starting dose of 100 and 140 mg once daily, respectively. Reappearance of hematological toxicity was observed in 3 patients and pancreatitis in one patient. Treatment was given at a lower dose and patients were followed. The median follow-up was 13 months and the median dose of dasatinib until achievement of complete cytogenetic remission (CCyR) was 60 mg daily (range = 20 to 120 mg). All four patients had achieved CCyR at a median of 4 months (range = 3 to 5 months) and among them, three had also achieved major molecular remission. We conclude that low-dose dasatinib therapy in intolerant patients appears safe and efficacious and may be tried before drug discontinuation.

Keywords: chronic myeloid leukemia, dasatinib/*administration & dosage, adverse events, treatment outcome

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Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder of blood stem cells.[1] The causative molecular defect is the BCR-ABL protein, which is encoded by the Philadelphia chromosome (Ph).[2] This genetic anomaly arises from an exchange of genetic material between chromosomes 9 and 22, which results in the fusion of the breakpoint cluster region (*BCR*) and the Abelson leukemia virus (*ABL*) proto-oncogene.[3,4] The resulting gene encodes a constitutively active protein kinase that activates a number of proteins involved in cell-cycle regulation that hasten cell division and affect DNA repair.[5–8] Imatinib, also known as Gleevec® (Novartis, Basel, Switzerland), is a selective inhibitor of not only ABL but also Kit and PDGFR kinases, and exerts significant antileukemic activity in the majority of CML patients.

According to the current National Comprehensive Cancer Network (NCCN) guidelines[9] and the European LeukemiaNet (ELN) recommendations,[10] a response outcome to imatinib therapy is classified as optimal, suboptimal, and failure based on the level of response achieved at various time points throughout the course of treatment using specific hematologic, cytogenetic and molecular criteria. Optimal responses proposed by the NCCN closely corresponding to the ELN recommendations and defined as the achievement of a CCyR after 12 months of imatinib at 400 mg daily. In patients with suboptimal responses to first-line imatinib, the use of high-dose (600 or 800 mg/day) is recommended as an alternative therapeutic option by both the ELN and the NCCN. Failure to achieve any cytogenetic response from standard-dose imatinib after 6 months of therapy or major cytogenetic response and a CCyR after 12 and 18 months of therapy, respectively, are considered treatment failure by the NCCN. In such cases, it is recommended that treatment should be changed for a second-generation tyrosine kinase inhibitor (TKI). These criteria became particularly important as several kinase targeted therapies with long half-lives were developed for the treatment of patients who fail or are intolerant to imatinib therapy.

According to the most recent results from the International Randomized Study of Interferon versus STI571 (IRIS) trial, the estimated overall survival for patients still on imatinib was 85% at 8 years, or 93% when only CML-related deaths or deaths prior to stem cell transplant were included. A total of 92% of the patients were free of disease progression. Among those who achieved CCyR, only 3% progressed during the 8-year follow-up.[11] Nevertheless, of the 259 patients receiving imatinib as front-line therapy who had treatment discontinuation, 30 (5.4%) and 77 (13.9%) patients stopped their therapy because of intolerance or unsatisfactory therapeutic effect, respectively. The inability of patients to tolerate treatment and the emergence of *BCR-ABL* mutations that reduced the binding affinity of imatinib prompted pharmaceutical research that led to the discovery of several similarly effective, targeted, second generation TKIs such as nilotinib (Tasigna, AMN107, Novartis, Basel, Switzerland) and dasatinib (SPRYCEL; Bristol-Myers Squibb, New York, NY).[12–14] Evidence from an in vitro study has indicated that nilotinib is 20 times more potent than imatinib against cells expressing the wild-type BCR-ABL.[15] Dasatinib is a multi-targeted kinase inhibitor that is structurally unrelated to imatinib and is able to bind and inhibit both the active and inactive conformations of ABL, resulting in 100- to 300-fold higher activity than imatinib for unmutated *BCR-ABL,* and greater inhibition against mutants with high levels of imatinib resistance (except for T315I and relative insensitivity to F317L).[15–17] Dasatinib is generally well tolerated. However, adverse events (AEs) associated with its use, such as pleural effusions, hemorrhage, and febrile neutropenia have been frequently reported in the advanced stage of the disease (reviewed by Wong[18]). The NCCN guidelines[9] recommend that at the onset of grade 3/4 thrombocytopenia (platelet count $<$50,000/mm), therapy with dasatinib should be held. Once the toxicity has resolved (platelet count $\geq$50,000/mm), dasatinib should be resumed at original starting dose if recovery occurs within 7 days or reduced one dose level if platelet count decreased to $<$25,000/mm for more than 7 days.

Attempts to identify the optimum and effective dose of dasatinib continue and include modification of scheduling, management of toxicity and dose optimization. To determine the optimum administration schedule, the efficacy, response and tolerability of dasatinib has been investigated in several clinical trials. It is now apparent that a scheduled

once daily starting dose of 100 mg offers an improved safety profile and shows similar efficacy for patients with chronic phase CML (CP CML) compared to a 70 mg twice daily dose.[19–21] The recommended dosage schedule for patients in the advanced phase of the disease is 140 mg once daily.[22,23] However, some intolerant patients may require a dose adjustment from 140 to 100 mg/day or from 100 to 80 mg/day to continue treatment and thus maintain control of their disease. Even at a dose of 80 mg/day, some patients require further dose reduction due to substantial toxicities. Because of the clinical difficulty posed by this subgroup, we report the effects of an unusually low dosage of dasatinib during the treatment of four patients (2 in chronic phase and 2 in accelerated phase) with proven efficacy almost identical to that seen with conventional dosage.

Case one

A 31-year-old man was admitted to our department in March 2008 with leukocytosis (WBC 88.900/mm³) and splenomegaly of CML. The patient was treated with imatinib mesylate at 400 mg/day in July 2008. One month after starting the therapy, the patient developed a grade (G) 4 thrombocytopenia (8.000/mm³ platelets) with epistaxis and needed a platelet transfusion. The patient had a therapy break of 4 months. In October 2008, after resolution of thrombocytopenia to the G1 level, he was restarted on a reduced imatinib dose of 300 mg per day, but therapy was again discontinued for thrombocytopenia G3 (26.000/mm³ platelets). In February 2009, because of severe intolerance to imatinib, dasatinib was started at a dose of 100 mg/day. After 2 weeks of treatment under this therapy, the patient developed a G4 thrombocytopenia. As a result, treatment was suspended until (March 2009) recovery to G1 (78.000/mm³) and then resumed at a dose of 80 mg/day. However, the patient experienced the same side effects one week after restarting dasatinib. The dose was then decreased to 50 mg/day with gradual increase of platelets. In June 2009, after 4 months of treatment, the patient achieved a CCyR. The patient continued the same dasatinib dose and in July 2009, the platelet count reached 130.000/mm³ and molecular analysis showed a *BCR-ABL/BCR* ratio of 0.01% indicating that the patient had achieved a major molecular response (MMR).

Case two

A 46-year-old male was admitted to our department in July 2008 with CP CML. The patient received imatinib at 400 mg/day in September 2008. This patient had two breaks in his imatinib therapy due to the recurring of G 3 thrombocytopenia. After the second break, the patient progressed to AP CML without evidence of mutations in the ABL kinase domain. In March 2009, dasatinib was prescribed to this patient at 140 mg/day and after four weeks of therapy, the patient developed G3 thrombocytopenia, after which we decided to maintain the therapy at a lower dose of 70 mg/day. In June 2009, after three months of treatment, the patient reached a CCyR and his thrombocytopenia improved to G1. To achieve MMR, we decided to increase the therapeutic dose to 80 mg/day in May 2010. By August 2010, on his last evaluation, this patient's *BCR-ABL/BCR* ratio showed 0.8%.

Case three

A 69-year-old male was admitted to our department in March 2009 with a history of CML, first diagnosed in August 2007 in Japan. Six months before the referral, he complained of fatigue, weight loss and splenomegaly. The patient had received hydroxyurea to control his leukocytosis. A diagnosis of AP CML was confirmed with the appearance of additional chromosomal aberrations besides the Ph chromosome (47XY, +8, t(9,22), add(13)(q33) in 20/20 metaphase analyzed) and, in March 2009, imatinib was initiated at a daily dose of 600 mg. After 1 month, the patient experienced G3 neutropenia (700/mm³) and G2 thrombocytopenia (62.000/mm³). The patient continued imatinib at the same dose with 300 µg granulocyte-colony-stimulating factor (G-CSF) added simultaneously every week to stimulate myelopoiesis. In October 2009, the patient experienced G3 thrombocytopenia (41.000/mm³) and his *BCR-ABL/BCR* ratio was 7.68% without any cytogenetic response after 6 months of therapy. At this time, sequencing of the BCR-ABL kinase domain revealed no evidence of mutations in the ABL kinase domain. Based on these results, the patient was, therefore, considered resistant to imatinib and, in November 2009, was placed on dasatinib at a daily dose of 140 mg. After the first 3 weeks of treatment, dasatinib was reduced

to 100 mg/day because of the occurrence of G2 thrombocytopenia (61.000/mm³). Two weeks later, his platelet count dropped to 50.000/mm³. At this time, dasatinib was lowered to a dose of 70 mg in an attempt to maintain a stable platelet count. However, after another 2 weeks, in January 2010, the patient developed G3 neutropenia (900/mm³) and his platelet count dropped to 26.000/mm³. At this time, the patient`s *BCR-ABL/BCR* ratio was 9.87%. As dasatinib was the only option for the treatment of this patient's disease, it was again reduced to a dose of 50 mg/day with G-CSF. In February 2010, the patient's *BCR-ABL/BCR* ratio was decreased to 0.81% and his platelet numbers started to increase gradually. As a result, G-CSF was stopped and the patient continued dasatinib at the same dose. Five months after initiation of dasatinib, in April 2010, cytogenetic analysis revealed a CCyR and complete disappearance of the initially detected additional chromosomal aberrations. In May 2010, dasatinib was increased to 60 mg once daily to achieve MMR and no toxicity was noted on follow-up examination. One month later, in June 2010, the patient achieved MMR, with a transcript ratio of 0.01%.

Case four

The patient, a 58-year-old man, was presented to our hospital in March 2009 with a clinical history of rheumatoid arthritis, hypertension, gastritis and chronic renal failure and undergoing conservative therapy. At presentation, a routine blood count showed leukocytosis with a left shift and physical examination revealed no splenomegaly. A diagnosis of CP CML was made after further laboratory studies and, in April 2009, imatinib was initiated at a daily dose of 400 mg. After a one month, despite a complete hematological response, the patient`s pancreatic enzymes elevated to G1 and then gradually increased in severity to G4 in May 2009. This result led to immediate treatment suspension. After a one month period of interruption, imatinib was resumed at the same dose. However, the patient experienced the same side effects again and treatment was permanently discontinued. One month later, the patient's pancreatic enzyme values returned to normal but he lost his hematologic response. At that time, dasatinib was initiated at a dose of 100 mg/day. During follow-up, the patient had two breaks in the dasatinib therapy at a daily dose of 100 mg and 40 mg because of recurring G2 and G4 pancreatitis, respectively. An abdominal computed tomography scan did not reveal any marked abnormality of the pancreas. After the second break, a 10-week interruption, the serum lipase level was returned to normal and dasatinib was reintroduced at a further reduced dose of 20 mg/day taken in combination with Pancrelipase (Creon) capsules. At a subsequent clinic visit, the patient presented with G2 pancreatitis and the treatment schedule and doses were maintained. In February 2010, the patient underwent a switch to alternate-day dasatinib at dosages of 20 and 40 mg every other day. In March 2010, after 3 months of taking a lower dosage (20 mg/day) of dasatinib, the patient achieved a CCyR and his *BCR-ABL/BCR* showed a ratio of 0.1%. The measurement of his transcript was repeated in August 2010 and confirmed the MMR (*BCR-ABL/BCR* ratio = 0.018%). At that time, the patient had mild pancreatitis with serum lipase level and was scored as grade 1.

Discussion

Dasatinib is a highly effective targeted therapy in patients with CML who are unresponsive to imatinib, or as an alternative where imatinib is poorly tolerated. As such, it provides a valuable therapeutic option for those patients who are at high risk for disease progression. Although dasatinib is generally well tolerated, serious toxicities can occur in some patients, even at a lower recommended dose of 80 mg/day, and can pose particular challenges to clinicians caring for this subgroup of patients. Patients intolerant of dasatinib and other TKIs are unlike those resistant to therapy; they often suffer increased treatment interruptions and compromised therapeutic benefits. Therefore, to fit an individual's unique profile, adjustment of dose on the basis of the patient`s response and tolerability is required. Our experience in this short case series demonstrate that dasatinib at a dose well below the minimum recommended dosage has clinical activity associated with only minor toxicity in 4 dasatinib-intolerant patients who had previously experienced imatinib-related hematological (3 cases) and non-hematological complications (1 case). At the time of initiation of

dasatinib therapy, two patients were in CP CML and the other two were in AP. All 4 patients had been initially treated with imatinib as a first-line therapy at either 400 mg/day or 600 mg/day and all but one developed hematological toxicities (Table 1). The same pre-existing complications that occurred during imatinib therapy were observed after crossover to dasatinib. It is possible that the complications manifested in our patients during imatinib therapy may have increased the likelihood of these abnormalities shortly after initiation of dasatinib. Alternatively, it is also possible that TKIs predisposed our patients to these AEs. In all patients, dasatinib, was the only second generation TKIs available at that time, had to be reduced to a lower dose because of the dose-limiting toxicity. The mean time to a CCyR in the first 3 patients was 3 and 5.5 months; similar to durations of <6 months that have been reported previously for standard doses.[21,24] Administration of dasatinib at a reduced daily dose thus induces remissions in a similar time frame compared with administration of a conventional dosage amount. Moreover, under continuous treatment with dasatinib under low dosage, there was progressive improvement of the platelet count in all of our first three patients, with progression to G1 thrombocytopenia (case 1 and 2) and complete normalization (case 3). Although the third patient developed G3 neutropenia with dasatinib, it

Table 1. Patient characteristics and responses to treatment.

	Case 1	Case 2	Case 3	Case 4
Age	31	46	69	58
Sex	M	M	M	M
CML Phase	CP	AP*	AP	CP
Imatinib (mg/day)	400	400	600	400
§Response to imatinib	CHR	PD	Failure	CHR
Imatinib associated AEs	G4 thrombocytopenia	G3 thrombocytopenia	G3 thrombocytopenia	G4 pancreatitis
Dasatinib starting dose (mg/day)	100	140	140	100
Dasatinib starting dose associated AEs	G4 thrombocytopenia	G3 thrombocytopenia	G3 thrombocytopenia	G4 pancreatitis
Mean daily doses of dasatinib until CcyR (mg/day)	46.25	93.3	65.45	*23.3
Median daily doses of dasatinib until CcyR (mg/day)	50	70	50	30
Time from dasatinib until CCyR (months)	4	3	5	*3
Intervention during dasatinib therapy	1st suspension for 2 weeks, dasatinib reintroduction at 80 mg/day 2nd suspension for 1 week, dasatinib reintroduction at 50 mg/day	Dose reduced to 70 mg/day	Dose reduced to 100, 70, and 50 mg	1st suspension for 2 weeks, dasatinib reintroduction at 40 mg/day 2nd suspension for 10 weeks, dasatinib reintroduction at 20 mg/day
Dasatinib best response and duration of response (months)	MMR (13)	CCyR (14)	MMR (2)	MMR (2)

Notes: *The patient progressed to AP during imatinib treatment (after two months of treatment interruption the patient had platelets <100.000 associated with left shift leukocytosis); *The mean dose and time from dasatinib until CCyR were considered from the reintroduction of dasatinib at a dose of 20 mg/day; §The remission status at the start of dasatinib therapy equally corresponds to imatinib response.
Abbreviations: M, Male; G, Grade; CP, Chronic phase; AP, Accelerated phase; PD, Progression of disease; AEs, Adverse events; CHR, Complete hematologic response; CCyR, Complete cytogenetic remission; MMR, Major molecular remission.

was easily managed by the weekly administration of G-CSF. The myelosupression can occur as a result of a sudden hematopoiesis suppression that was maintained by Ph+ cells without equilibrium of the reappearance of the Ph- cells. Thus, we speculate that lower doses of dasatinib can correct this disequilibrium.

The fourth patient developed G4 pancreatitis after being initiated on imatinib mesylate and recurred with the same symptoms after switching to dasatinib even at the lower dose of 40 mg/day. The patient had no risk factors for pancreatitis and was taking no medications known to cause pancreatitis other than imatinib. The reason why it was unlikely for this patient to develop pancreatitis due to CML is because the onset of this complication appeared during the imatinib treatment and then gradually improved upon suspension of therapy. De novo appearance of symptoms appeared after initiation of dasatinib. Pancreatitis is an extremely rare adverse event which occurs after the use of TKIs.[23,25–29] The pathophysiology of TKIs-induced pancreatitis remains speculative, but has been proposed by Plandari and colleagues[26] to be due either to the inhibition of c-abl, which might interfere with the molecular mechanisms that regulate pancreatic cell death and thus induce pancreatic damage, or to the indirect effect of the drug on the release of calcium from the intracellular acinar stores, which regulate exocrine pancreatic secretion, and may enhance the accumulation of fatty acid inside the pancreatic acinar cell, which disturbs exocytosis.

At the time of this report, three of the four patients we treated had achieved MMR. It is possible that the greater potency of *BCR-ABL* inhibition of dasatinib compared to imatinib contributed to the induction of remissions in our patients. Because of its greater potency (325-fold), it has previously been reported that exposure to low or subnanomolar concentrations of dasatinib is sufficient to commit cell lines expressing BCR-ABL to apoptotic cell death.[15,16] These results may help to explain the improved tolerability and efficacy observed in our patients.

An increasing number of investigators are exploring the use of a lower dose intensity of dasatinib for the treatment of therapy intolerant patients. In one recent study, the frequency and significance of dose reductions and treatment holidays among 280 patients treated with 2nd generation TKIs were retrospectively analyzed.[30] The results revealed that 176 (63%) of these patients required treatment interruptions and/or dose reduction at least once during therapy. The authors conclude that lower doses of dasatinib and nilotinib may potentially have similar efficacy in the therapy of CML as standard doses. In another small study, Bergeron et al[31] investigated pleural and pulmonary complications in 40 patients who received dasatinib (70 mg twice daily) for imatinib resistance or intolerance. Dasatinib treatment was interrupted in eight patients, either immediately after diagnosis of lung involvement (five patients), or after a course of diuretics (three patients). After treatment holidays, lung abnormalities were resolved in all cases and did not recur in three out of four patients when dasatinib was reintroduced at a dose of 40 mg twice daily. In addition, Breccia et al[32] treated a 34-year-old Ph+ CML female patient who had a molecular relapse after haploidentical BMT with chronic liver GVHD and was severely intolerant to both imatinib and dasatinib at a standard dose; she had a CMR to dasatinib at a reduced dose of 20 mg/day without serious adverse events. A recent case report published by Yamaguchi et al.[33] described a successful treatment of a 70-year-old man with CML who developed a megakaryoblastic crisis concomitant with myelofibrosis despite imatinib therapy with dasatinib at a starting dose of 80 mg/day.

Despite the successful clinical response in these patients, conclusions drawn from this series should be interpreted with caution and considered tentative until experimental studies to define the minimum effective dose and optimal dosing schedule for dasatinib-intolerant patients are carried out. However, our series lend support to previous reports that showed a comparable efficacy of standard and low-dose dasatinib with very minor toxicities; thus, for patients intolerant to dasatinib at a standard dose, a gradual dose reduction may be tried before drug discontinuation.

Authors' contributions

MS was responsible of the clinical management of patients, acquisition of data, drafting the manuscript; SS was responsible of the scientific revision,

discussion and editing of the manuscript; IB was responsible of the molecular monitoring and interpretation of data; MC, FS, FX and CBB were involved in clinical management of patients and interpretation of data; PED was supervisor of clinical management of patients and interpretation of data. All authors read and approved the final manuscript.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material. Written consent was obtained from the patient or relative for publication of this study.

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