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ORIGINAL ARTICLE

Improved tolerability by a modified intermittent treatment schedule of dasatinib for patients with chronic myeloid leukemia resistant or intolerant to imatinib

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Abstract Intermittent dosing of dasatinib with a once daily regimen has been shown to reduce side effects while preserving clinical efficacy in early and advanced phase chronic myeloid leukemia (CML). Yet, hematologic toxicity and fluid retention demand a dose modification or treatment discontinuation in selected patients. Patients resistant or intolerant to imatinib were retrospectively evaluated based on the toxicity-guided administration of a dose-reduced dasatinib regimen. Patients were treated with an on/off regimen (3 to 5 days on, 2 to 4 days off) to allow regression of dasatinib-dependent *off-target* toxicity. Patients were followed up by routine hematologic and cytogenetic assessment and molecular monitoring to safeguard clinical response to the altered drug schedule. Thirty-three CML patients primarily in chronic phase with imatinib intolerance (n=11) or resistance (n=22) were investigated. Nonexclusive reasons for dose reduction were hematologic toxicity (17/33, 51 %) and pleural effusions (18/33, 55 %). On/off treatment with a weekend drug holiday significantly reduced pleural effusions and hematologic toxicity. Eighteen of 31 (58 %) patients showed effective disease control despite reduced total weekly dasatinib doses, either demonstrated by achieving an improved response level (12/31) or keeping the response level achieved by conventional continuous dosing (6/31). Of note, 10/12 patients with subsequently improved response have been treated for a minimum of 6 months with continuous dosing dasatinib regimens without having achieved the response level achieved after allowing drug holiday. Weekend treatment interruption of dasatinib allows continuation of dasatinib treatment for patients suffering from side effects. These data mandate prospective investigation of alternative intermittent targeting regimens.

Keywords Dasatinib · Resistance · CML · Tolerability · Toxicity · Dosing

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Introduction

Dasatinib (Sprycel™) is an oral multitargeted BCR-ABL inhibitor indicated for treatment of patients with chronic myeloid leukemia (CML) or Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia [1]. Dasatinib is approved for treatment of patients with newly diagnosed chronic phase CML and for the treatment of patients in all phases of CML, who are resistant or intolerant to previous treatment, including imatinib [2, 3].

Dasatinib has approximately 300-fold improved affinity, but reduced selectivity for BCR-ABL as compared to

imatinib or the imatinib-derivative nilotinib [4, 5]. In line with short plasma level with a half time of 3 to 5 h, pharmacodynamic monitoring of actual BCR-ABL inhibition in patients treated with dasatinib revealed short duration of BCR-ABL substrate inhibition with reactivation of kinase activity as early as 8 h after treatment onset [3, 6]. This suggested that a twice daily dosing (BID) regimen (2× 50 mg) would be necessary for continuous kinase inhibition, which was believed to be a dominant response-determining variable [7]. However, clinical results demonstrated equal disease control with reduced toxicity in patients treated with a once daily (QD) regimen (1×100 mg) [3]. A dose optimization study confirmed this initial observation leading to modification of the initially approved treatment schedule in chronic phase (100 mg QD) as well as in accelerated phase (AP) and blast crisis (BC) (140 mg QD) [8, 9]. Dasatinib-induced side effects require treatment interruption or dose modification in particular due to hematologic toxicity or pleural effusions [10]. Toxicity rates are higher in patients treated with second-line compared to first-line patients with the marked difference that patients in the second-line study had a median age of 59 vs 47 years in the first-line DASISION study [11, 12].

Here, we report on the clinical experience with a cohort (n=33) of CML patients in chronic phase treated with dasatinib for imatinib resistant or intolerant disease. Patients were selected based on the toxicity-guided administration of a dose-reduced dasatinib regimen that allowed a 2- to 4-day treatment interruption for toxicity management, which was chosen due to the experimental evidence that sufficient peak plasma levels might be more important to induce leukemic cell kill than continuous daily dosing [13].

Methods

Patients and study design

A retrospective analysis of 33 patients was performed by chart analysis. All patients were either intolerant or resistant to former treatment with imatinib. Patients were selected based on the toxicity-guided administration of a dose-reduced dasatinib regimen. Toxicity was scored using the Common Terminology Criteria of Adverse Events (version 3.0, accessible via http://ctep.cancer.gov). Patients treated with a weekly on/off regimen only (3 to 5 days on, 2 to 4 days off) were included. Patients were followed up by routine hematologic assessment, cytogenetics, and molecular monitoring. Clinical response was assessed using the European LeukemiaNet criteria [14]. Complete cytogenetic response refers to no Ph+ metaphases; major cytogenetic response defines 1 to 35 % Ph+ metaphases. Molecular response was assessed at baseline and every 2 to 3 months thereafter by determining the *BCR-ABL* mRNA transcript level according to the international scale (IS) by quantitative RT-PCR (Q-RT-PCR) from total peripheral blood leukocytes [15]. *BCR-ABL* transcripts at a level more than 0.1 to 1.0 % IS are defined as minor molecular response; *BCR-ABL* transcript levels of ≤0.1 % IS indicate major molecular response (MMR); and undetectable *BCR-ABL* by Q-RT-PCR and nested RT-PCR with at least 32,000 *ABL* transcripts per volume cDNA are referred to as molecular remission with a sensitivity of at least 4.5 orders of magnitude ($MR^{4.5}$) [16].

Resistant patients were regularly screened for BCR-ABL mutations. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Detection, quantification, and mutation analysis of BCR-ABL

RNA extraction, cDNA synthesis, and qualitative and quantitative BCR-ABL PCR were performed as described previously [17, 18].

Mutation analysis was performed by denaturing high-performance liquid chromatography as described by Soverini et al. [19] with minor modifications of primers and temperatures [20].

Data analysis

Statistical analysis was performed to assess significant differences between treatment conditions using the t test. Data analysis was performed using the GraphPad Prism version 4.00 for Windows, GraphPad Software, San Diego CA, and MS Excel (Seattle, WA).

Results

Patients' baseline characteristics

Thirty-three patients were investigated. General patient characteristics are given in Table 1. The median age was 66 years (range, 39–81 years) with a male/female ratio of 1.54 which reflects general population-based registry data of CML patients (18). The majority of patients were treated for chronic phase CML (n=30), two had accelerated phase disease and one patient was in blast crisis. The median time from diagnosis was 38 months with up to 5 (median, 3; range, 1–5 months) preceding therapeutic regimens. Twenty-two patients were treated with dasatinib for imatinib-resistant disease, 11 patients due to intolerance (skin reaction n=8; liver toxicity n=2; pulmonary toxicity n=1). BCR-ABL kinase domain mutations known to induce

Table 1 Patient characteristics prior to intermittent dosing

No.	Sex	Age (years)	Time from Dx	CML phase	Prior treatment	Reason for second-line DA	DA dose (mg)
1	m	51	24	CP	HU, IM	R (M244V)	50 BID
2	m	71	37	CP	HU, IFN, IM	R (G250E)	50 BID
3	f	69	118	CP	HU, IFN, IM	R (E255K)	50 BID
4	m	63	23	CP	HU, IM	R (M244V)	70 BID
5	m	68	12	CP	IM	I (skin III-IV)	50 BID
6	f	69	189	CP	HU, IFN, IM	R (no CyR)	50 BID
7	m	53	38	CP	HU, IFN, IM	R (no MCyR)	70 BID
8	f	64	99	CP	HU, IFN, IM, HHT	R (no MCyR)	50 BID
9	f	60	22	CP	IM	I (Hep III)	50 BID
10	f	44	128	CP	HU, IFN, IM	R (no CyR)	70 BID
11	f	73	114	CP	HU, IFN, IM	I (skin III)	50 BID
12	m	61	124	AP	HU, IFN, IM, BU	R (M351T)	70 BID
13	m	81	103	CP	HU, IM	R (F359I)	50 BID
14	m	47	21	CP	HU, IM	R (no CyR)	50 BID
15	f	74	187	CP	HU, IFN, IM	R (H396R, Y253H, E355G)	50 BID
16	f	72	60	CP	HU, IFN, IM	I (skin III)	n/a
17	m	64	172	CP	HU, IFN, IM	R (E255V)	50 BID
18	m	69	172	AP	BU, Cy, HU, IFN, IM	R (loss CHR)	50 BID
19	f	67	14	CP	IM, IFN	I (skin III)	50 BID
20	m	70	9	CP	HU, IM	R (no CyR), I (skin III)	70 BID
21	m	44	70	CP	HU, IFN, IM	R (F359I)	70 BID
22	f	67	32	CP	IM, IFN	I (skin III)	100
23	m	65	22	CP	HU, IM, IFN, Ara-C	I (skin III)	70 BID
24	f	67	40	CP	HU, ICE, IFN, IM	I (hepar III)	70 BID
25	m	39	129	CP	HU, IFN, IM	R (E255K)	70 BID
26	m	78	72	CP	IFN, HU, Ara-C, IM	R (L248V)	70 BID
27	f	60	61	BC	IFN, HU, IM	R (D276G)	70 BID
28	m	49	8	CP	HU, IM	I (ANC III)	50 BID
29	f	66	11	CP	IM. HU	I (pulmo III)	50 BID
30	m	53	12	CP	IM	R (no MCyR)	80
31	m	74	12	CP	IM	R (no MCyR)	80
32	m	76	6	CP	IM	I (skin III)	80
33	m	57	15	CP	IM	R (F359V)	80
Median		66	38				
Range		39–81	6–189				

f female, *m* male, *HU* hydroxyurea, *IFN* interferon-α, *IM* imatinib, *DA* dasatinib, *I* intolerance, *R* resistance, *CyR* cytogenetic response, *MCyR* major cytogenetic response, *BID* bis in die, twice daily, *n/a* not available, *Dx* diagnosis

resistance to imatinib were found in 13/22 (59 %) patients. Other reasons triggering change of treatment to dasatinib were not having achieved cytogenetic response in due time or loss of hematologic response [14].

Most patients received dasatinib on a twice daily regimen with 16 patients treated with 50 mg BID, 11 patients treated with 70 mg BID, 1 patient received 100 mg QD, and 4 patients received 80 mg QD. Duration of conventional dasatinib treatment prior to interval treatment was 313 days (median; range, 46–924 days).

Toxicity and response to dasatinib prior and after schedule modification

Dose adjustment of dasatinib was primarily necessary due to hematologic toxicity or pleural effusions, which in most cases were symptomatic grade 2–3 effusions (18/33) (Table 2). Hematologic toxicity with up to grade 4 thrombocytopenia was apparent in 17/33 (51 %) patients and anemia occurred in 7/33 (21 %) patients. Overall, 27 patients (82 %) suffered from grade 3 to 4 side effects. Nine

Table 2 Toxicity and response to treatment, intermittent dosing

No.	DA dose(mg) (continuous)	Toxicity	Best response	DA dose (mg) (intermittent)	Toxicity	Best response
1	50 BID	PLT IV	SD	50 BID 5×	PLT III	SD
2	50 BID	PE III	CCyR	70 4×	PE II	MMR
3	50 BID	Hb II, PLT II	minCyR	100 5×	PLT I	MMR
4	70 BID	PE III	MMR	100 5×	PE 0	$MR^{4.5}$
5	50 BID	PE III	$MR^{4.5}$	90 4×	PE II	$MR^{4.5}$
6	50 BID	PLT IV	CHR	100 4×	PLT III	CHR
7	70 BID	PE III	MMR	100 5×	PE II	MMR
8	50 BID	PE III	MMR	50 BID 5×	PE II	MMR
9	50 BID	PE II, Skin II	$MR^{4.5}$	40 BID 5×	PE 0, Skin 0	$MR^{4.5}$
10	70 BID	PE III	MMR	50 BID 5×	PE I	MMR
11	50 BID	PE III	n/a	50 BID 5×	PE II	n/a
12	70 BID	PLT III-IV, Hb III	RTC	40 BID 4×	PLT I, Hb I	CHR
13	50 BID	PE III, PLT IV, Hb II	SD	40 BID 4×	PE III, PLT I, Hb I,	MCyR
14	50 BID	PLT III	SD	50 BID 5×	PLT II	SD
15	50 BID	PE II	minCyR	50 BID 5×	PE I	CHR
16	n/a	PLT III, Hb II, PE III	MCyR	40 BID 5×	PLT I, PE I	MCyR
17	50 BID	PLT III	n/a	50 BID 5×	PLT I	n/a
18	50 BID	PLT IV, Hb IV	minCyR	100 5×	PLT 0, Hb I	RTC
19	50 BID	PE III	MMR	70 5×	PE II	$MR^{4.5}$
20	70 BID	PLT III	MCyR	50 BID 5×	PLT II	CCyR
21	70 BID	PE III	MMR	70 5×	PE II	MCyR
22	100	WBC III, PLT II, Hb II	CHR	80 4×	WBC II, PLT I,	CCyR
23	70 BID	PE III	MMR	50 BID 5×	PE I–II	MMR
24	70 BID	PLT III	MCyR	50 BID 5×	PLT I	$MR^{4.5}$
25	70 BID	PLT III, WBC II	n/a	50 BID 5×	PLT I, WBC I	MCyR
26	70 BID	PE III, PLT II, Hb II	n/a	50 BID 4×	PE III, PLT I, Hb II	MCyR
27	70 BID	PE III	CCyR	50 BID 5×	PE III, Hb III	CCyR
28	50 BID	PLT III	minCyR	50 BID 5×	ANC I, PLT I	$MR^{4.5}$
29	50 BID	PE III	MMR	100 5×	PE II	$MR^{4.5}$
30	80	PLT III, ANC IV	CCyR	100 5×	PLT 0, WBC I	$MR^{4.5}$
31	80	PLT III, ANC III	CCyR	100 5×	ANC I, PLT II	CCyR
32	80	Skin III	CCyR	100 5×	Skin I	$MR^{4.5}$
33	80	PE II	n/a	100 5×	PE 0	CCyR

DA dasatinib, *PLT* thrombocytopenia, *Hb* anemia, *PE* pleural effusion, *ANC* absolute neutrophil count, *SD* stable disease, *CCyR* complete cytogenetic response, *minCyR* minimal cytogenetic response, *MCyR* major cytogenetic response, *MMR* major molecular response, $MR^{4.5}$ molecular remission with a sensitivity of 4.5 orders of magnitude (International Scale)

patients had achieved MMR at least at one occasion as best response.

The median weekly dose of the dasatinib weekend holiday schedule was 500 (range, 320–500 mg) as opposed to 700 (range, 560–980 mg) prior to the change in drug scheduling. Assessment of toxicity after switching patients on the 5 days on/2 days off (5+2) regimen (n=26) or the 4 days on/3 days off (4+3) regimen (n=7) reduced the toxicity CTC score by median 1 (3 vs 2, pleural effusion) or 2 (3 vs 1, hematologic toxicity) grades, respectively (Fig. 1). Due to the nature of this retrospective analysis, data to calculate the exact time achieving a reduced grade of toxicity were not available. Yet in most patients, amelioration of side effects was achieved within weeks.

For response analysis, two patients were excluded due to early stem cell transplantation (SCT) or insufficient response assessment (lost to follow-up). Those patients did not show any sign of progression prior to SCT. The total of 31 evaluable patients was grouped into three categories:

1. Patients showing stable disease control without having achieved sustained molecular response or showing resistant disease after transient disease control (n=13; 42 %). Twelve of 13 (92 %) patients were on second-line

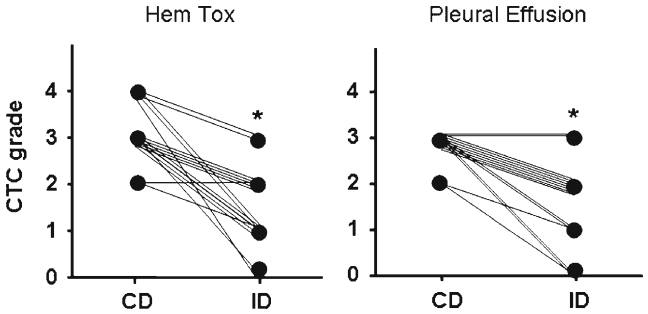

Fig. 1 Reduction of toxicity as scored by CTC grades by weekend drug holiday from dasatinib. Hematological toxicity and pleural effusion was scored prior to and after switching patients from continuous dosing dastinib (*CD*) to intermittent dosing with weekend drug holidays (*ID*) and recorded in 3 months intervals. Time to improvement was not systematically documented and is hence not reflected in this figure. Minimal toxicity level recorded in patient charts was used for analysis. Every single patient is shown by a *line* that depicts the change of CTC grade. A *t* test was performed to detect statistical significance (*$p<0.05$)

dasatinib due to resistance to imatinib with 6/13 patients tested positive for kinase domain mutations prior to dasatinib treatment. At progression, six new mutations (T315I, $n=2$; F317L, $n=3$; L248V, $n=1$) known to induce resistance against dasatinib were recovered. Three of 31 progressed to advanced phase CML ($n=1$, AP; $n=2$, BC).

2. The second cohort ($n=6$) represents patients who had to be treated by weekly interval treatment due to toxicity while being in MMR. These patients have a median documented follow-up of 33 months (range, 9–72 months), with none of them loosing MMR. Of note, four of six patients developed improved molecular response with achievement of $MR^{4.5}$.
3. The third group represents 12/31 (39 %) patients who had not achieved desirable surrogate monitoring end points on continuous dosing and showed improved response quality while on weekly interval treatment with a median documented follow-up of 51 months (range,18–8 months). Of note, 10/12 patients with improved response have been treated for a minimum of 6 months with continuous dosing dasatinib regimens without having achieved the response level observed after allowing modified intermittent dosing. Patients with maintained or improved response on interval treatment overall make 58 % (18/31) of the study cohort, 44 % (8/18) of which were treated with dasatinib due to resistance to imatinib. Sixteen of 18 (89 %) patients achieved or maintained MMR or $MR^{4.5}$.

Discussion

Intermittent daily targeting with the multikinase inhibitor dasatinib has been shown to reduce toxicity without impairing the efficacy of dasatinib [8, 9]. These clinical data coincided with various reports on the in vitro activity of dasatinib against BCR-ABL-transformed cells suggesting that the transient potent inhibition of BCR-ABL irreversibly induces apoptosis [13, 21]. Thus, the dogma fueled by murine models of CML that continuous target inhibition is a prerequisite for effective leukemic cell kill can no longer be upheld for dasatinib, which represents a different class of ABL-targeting inhibitors with reduced selectivity and enhanced potency [5, 22, 23]. Furthermore, dasatinib in comparison to imatinib, which has a plasma half-life of 19 h, has a significantly shortened plasma half-life of 3 to 5 h preventing patients from repetitive subtherapeutic drug levels that might promote the development of resistance [24, 25].

Our retrospectively analyzed cohort of patients exposed to a reduced weekly dose of dasatinib for the management of dasatinib-induced toxicity confirms these clinical and laboratory observations in that our selected patients requiring dose adjustments seem to benefit from weekend drug holiday not only with regard to the management of toxicity, but also with regard to optimizing disease control in a substantial subgroup (39 %). Whereas reduced severity of toxicity can be expected at a reduced weekly dose, it is notable in our view that patients with stable or improved response representing 58 % of the analyzed population achieve response levels that have not been achieved prior to interval treatment (star symbols, Fig. 1c of the electronic supplementary material). Though not formally proven, we hold two factors accountable for this finding: first is treatment without toxicity-triggered treatment interruptions that lasted weeks or sometimes months and second is high enough daily dosing in order to achieve potent transient inhibition of BCR-ABL to irreversibly induce apoptosis. Since our study was not prospectively designed, these hypothesis-generating findings need to be confirmed by a prospectively designed protocol.

The weakness of this study lies in its anectodical collection of affected patients. Baseline patient characteristics however indicate that these patients reflect a real-life situation, and not a distinct study population, which usually consists of patients with a 10 to 15 years lower median age [26]. The DASISION study group reported on the randomized first-line treatment of CML patients with dasatinib or imatinib [2]. In this study, only 8 % were ≥65 years, whereas our study population had a median age of 66 years. Thus, the toxicity profile with 10 % pleural effusions in the first-line study might not reflect daily medical care reality outside of clinical studies. As the prevalence of CML constantly increases through prolonged survival in the TKI era, it will additionally be important to focus on the elderly population treated with dasatinib, taking into account comorbidities and susceptibility to toxic side effects which seem to be higher as the disease and the age of the patients increases [26, 27].

Hence, alternate scheduling of dasatinib with weekend holidays has its rationale from laboratory and pharmacological data. This study analyzing patients affected by toxicity mandating dose reduction confirms this rationale clinically. Our subgroup of patients showing improved response after having been switched to weekend drug holiday let us speculate that patients generally may benefit from this alternate schedule. Drug holiday may increase compliance, which has recently come into focus for successful long-term disease control of CML [28]. Thus, the alternate dasatinib schedule should be tested prospectively in randomized studies in first-line therapy to further improve the management of CML patients.

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Conflict of interest AH received research support and honoraria by BMS, Novartis, ARIAD, and Pfizer. PL received speaker's honorarium and travel support by BMS and Novartis. BMS is the manufacturer of dasatinib.

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