



Dasatinib May Override F317L BCR-ABL Kinase Domain Mutation in Patients with Chronic Myeloid Leukemia

Dasatinib F317L BCR-ABL Mutasyonu Olan Kronik Miyeloid Lösemi Hastalarında Etkili Olabilir

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To the Editor,

The most common mechanisms for resistance in patients with chronic myeloid leukemia (CML) receiving imatinib mesylate are BCR-ABL kinase domain (KD) mutations. The mutations are stratified according to in vitro 50% inhibitory concentration (IC₅₀) values. The F317L KD mutation has been shown to induce a 9- to 13.5-fold increase of dasatinib IC₅₀ with respect to wild-type BCR-ABL in cellular assays [1]. The pharmacokinetic data showed that F317L is predicted to be moderately sensitive to dasatinib [2]. Jabbour et al. [3] published data on a cohort of 20 CML patients with F317L mutation and evaluated the characteristics and outcomes of these patients with tyrosine-kinase inhibitor (TKI) therapy. Among these 20 patients, F317L was detected in 12 after imatinib failure and in 8 after dasatinib failure. In the post-imatinib failure group, 3 patients received dasatinib. The best achieved response was partial hematologic response in 1 and complete hematologic response (CHR) in 2. Müller et al. [4] also reported the results of analysis of original dasatinib phase 2/3 trial data according to pre-existing mutations. Of the 402 patients with baseline KD mutations, 14 had F317L mutations; 13 (93%), 2 (14%), and 1 (7%) achieved CHR, major cytogenetic response (MCyR), and complete cytogenetic response (CCyR), respectively. None of the patients achieved major molecular response (MMR).

Among our CML cohort, we identified KD mutations by the denaturing high performance liquid chromatography sequencing method as described before [5]. In the literature, it has been recently demonstrated by our group as well as by some others that there are CML patients with F317L mutation who achieved and maintained both CCyR and MMR with dasatinib after imatinib failure (Table 1) [6,7,8,9].

Dasatinib is known to have significant therapeutic activity against the Src kinases, and this is responsible for several of its “off-target effects”. Pulmonary toxicity [i.e. pleural effusion (PE)] following dasatinib use can be observed in CML patients [10]. Lymphocytosis in CML patients receiving dasatinib might have contributed to therapeutic efficacy, and Mustjoki et al. [11] showed a strong association between clonal T/NK cell expansion and lymphocytic PE under dasatinib therapy and prolonged stable responses in patients with advanced Ph-positive leukemias. Among the 4 CML cases described in the literature with F317L in which MMR was achieved with dasatinib, 3 had episodes of reversible dasatinib-induced PEs and modest lymphocytosis was seen in 1 (Table 1). These clinical and laboratory findings may be attributed to the good response in these patients.

In conclusion, evidence indicating the resistance of the F317L mutation to TKIs mainly comes from in vitro

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Table 1: Characteristics of CML patients with F317L mutation with MMR under dasatinib published in the literature.

Author, year	Age in years/sex	CML stage at the start of imatinib	Best response to imatinib	Response duration to imatinib, months	Duration of imatinib treatment, months	KD mutations other than F317L	CML stage at imatinib failure	Dasatinib dose, mg/day	Duration of dasatinib treatment, months	Best response to dasatinib	Off-target effects of dasatinib	Follow-up after imatinib failure, months
1 Faber et al., 2010 [6]	52/M	L-CP	CCyR	27	42	E279K and H396R	CP	140	20	CCyR and MMR	PE and lymphocytosis	35
2 Oyekunle et al., 2011 [7]	59/F	L-CP	CHR and mCyR	25	31	H396R	CP	140	54	CCyR and MMR	PE	60
3 Eskazan et al., 2011 [8]	45/F	E-CP	CCyR and MMR	38	38	none	CP	100	38	CCyR and CMR	PE	38
4 Intermesoli et al., 2011 [9]	40/M	L-CP	CCyR	36	54	E255K	CP	140	34	CCyR and CMR	none	66

M= male, F= female, L-CP= late chronic phase, E-CP = early chronic phase, CP= chronic phase, CCyR= complete cytogenetic response, MMR= major molecular response, CMR= complete molecular response, mCyR= minor cytogenetic response, DAS= dasatinib, PE= pleural effusion.

studies. Since mutations are classified on the basis of their in vitro sensitivity to TKIs, the in vivo outcomes may not be in accordance with in vitro studies in every case. The presence of the F317L KD mutation may not uniformly predict poor outcomes in CML patients mainly on dasatinib. Outcomes may be related to a complex interplay of several factors possibly including the off-target effects of the TKI. It is important to carefully investigate and monitor individual patients, and although a switch to a TKI with better in vitro potency against a mutation may improve outcome, this strategy might not always be necessary, especially if the patient is in durable cytogenetic or molecular response.

Conflict of Interest

None of authors of this paper has any conflicts of interest, including specific financial interests, relationships, and/or affiliations, relevant to the subject matter or materials included in this manuscript.

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