

# Effective Molecular Monitoring and the Proper Management of Pleural Effusion During the First-Line Dasatinib Administration in CML

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## ABSTRACT

Dasatinib is considered an effective treatment agent in imatinib-resistant and newly diagnosed chronic phase CML patients. Patients receiving dasatinib 100 mg once daily regime suffered significantly fewer thrombocytopenia and pleural effusion events than those receiving 70 mg twice daily. Effective molecular monitoring and the proper management of pleural effusion during the first-line dasatinib administration in CML are essential. Pleural effusion may develop any time of the treatment and is easily managed by treatment interruption, dose reduction and supportive therapy. In this article, we intended to assess the rational of managing CML and pleural effusion that successfully managed with dose reduction and supportive care.

**Keywords:** Dasatinib, First-line therapy, Chronic myeloid leukemia, Pleural effusion

## ÖZET

### Kronik Myelositler Lösemide Birinci Basamak Tedavi Sırasında Oluşan Plevral Efüzyonun Yönetimi ve Etkin Moleküler İzlem

Dasatinib, imatinibe dirençli ve yeni tanı almış kronik faz KML hastalarında etkin bir tedavi ajanı olarak düşünülmektedir. Günde 100 mg tek doz dasatinib tedavisi alan hastaların günde 70 mg iki kez tedavisi alanlara göre anlamlı oranda daha düşük trombositopeni ve plevral efüzyon geliştirdikleri gösterilmiştir. KML'de moleküler monitörizasyonun dikkatli yapılması ve ilk sıra dasatinib verilen hastalarda plevral efüzyonun yönetilmesi büyük önem taşımaktadır. Plevral efüzyonun dasatinib tedavisinin herhangi bir zamanında ortaya çıkabilmekte ve doza ara verme, doz azaltma, ve destek tedaviler ile kolaylıkla yönetilebilmektedir. Bu çalışmada, KML ve plevral efüzyonun başarıyla yönetimine ilişkin moleküler yöntemler araştırılacaktır.

**Anahtar Kelimeler:** Dasatinib, İlk-basamak tedavi, Kronik miyeloid lösemi, Plevral efüzyon

## INTRODUCTION

Dasatinib (SPRYCEL; Bristol-Myers Squibb, New York, NY) is a multi tyrosine kinase inhibitor (TKI), such as BCR-ABL, PDGFR- $\beta$ , c-kit, and of SRC-family kinases<sup>1</sup> and approved for first (approved in the US and Europe since 2010) and second line therapy in all phases of Chronic Myeloid Leukemia (CML) (approved in the US and Europe since 2006). Dasatinib is also indicated for Ph positive-Acute Lymphoblastic Leukemia (ALL) and has good central nervous system penetration in managing Ph<sup>+</sup> intracranial leukemia.<sup>2</sup>

Dasatinib showed significant efficacy in patients with CP-CML who were resistant or intolerant to imatinib.<sup>3,4</sup> According to two year follow up data of the START-C trial (n= 387) indicated that overall CHR, MCyR, CCyR, and MMR rates were 91%, 62%, 53%, and 47%, respectively. 88 % of these patients have maintained their MCyR at 24 months. The over-all survival (OS) and progression-free survival (PFS) rates were presented as 94% and 80%, respectively.<sup>5,6</sup> In CA180-034 dose-optimization randomized study (n= 670), 100 mg QD study arm showed similar efficacy results regarding CCyR (50 % vs. 54 %), MCyR (63% vs.61%), PFS (80% vs. 76%), and OS (91% and 88%) rates versus patients who received 70 mg dasatinib BID at 24-month.<sup>7</sup> OS at 60-month was 78% and transformation to AP/BP on study was 0% (n= 0).<sup>8</sup>

In vitro, dasatinib has 325-fold greater pharmacologic potency than imatinib in unmutated BCR-ABL kinase.<sup>9</sup> Dasatinib may improve response rates in the first-line therapy because the increased inhibition of BCR-ABL provides a better clinical response<sup>10</sup> and dasatinib has resulted in high rates of CCyR and survival rates in second-line therapy of CML.<sup>4,8</sup> The DASISION study (Dasatinib versus Imatinib Study in Treatment-Naive CML Patients) compared dasatinib and imatinib in the first-line treatment of chronic-phase CML and study results at 12-month indicated significantly higher and faster rates of CCyR and MMR.<sup>11</sup> Dasatinib, 100 mg daily, was also associated with a lower incidence of any-grade pleural effusion; fewer patients required dose interruption, dose reduction, and toxicity-related discontinuation in the second line usage.<sup>8</sup> However, physicians may still think that dasatinib-tre-

ated chronic myeloid leukemia patients are at risk for the development of pleural and pericardial effusions for the first-line treatment. In this paper, we would like to emphasize that pleural effusion occurring during dasatinib treatment is easily managed by treatment interruption and supportive therapy.

## MATERIALS, METHODS AND RESULTS

The molecular study protocol was reviewed by the ethics committee. All patients gave written informed consent. BCR-ABL transcripts level assessment was performed by real-time quantitative polymerase chain reaction (RT-Q-PCR) according to suggested procedures and recommendations. BCR-ABL transcript levels were expressed as a percentage according to the IS, taking advantage of the ongoing international initiatives that allow researchers to standardize the quantitation of BCR-ABL transcripts through the use of a conversion factor and consequently to express their results according to the IS. The reference laboratories that performed most of the RT-Q-PCR analyses on this study and that were responsible for the validation of the results performed in central laboratory of DASISION. Representative samples were cross-checked in the laboratory. The materials, the reagents, and the methods that were used were developed within the international collaborative studies for the harmonization of BCR-ABL mRNA quantification.

Molecular technique has been applied to a representative CML patient. This typical patient was a 64-year-old Turkish female applied to our Hematology Clinic with leucocytosis which was detected during routine blood analysis. Her complete blood count (CBC) showed hemoglobin (Hb) of 12.7 g/dL (normal range: 12.00-18.00), mean corpuscular volume (MCV) 85.6 fL (normal range: 80.00-100.00). Her platelet count ( $575 \times 10^3/\mu\text{L}$ ) (normal range: 150.00-450.00) and white blood cell count (WBC) were high ( $89.8 \times 10^3/\mu\text{L}$ ) (normal range: 3.60-10.00) with 53.0% segmented neutrophils, 20.0% band neutrophils, 10.0% lymphocytes, 8.0% monocytes, 2.0% basophils, 2.0% metamyelocytes, 4.0% myelocytes, and 1.0% blasts. The biochemical assays revealed a mild increase in GGT (47 U/L [normal range: 5-36]) and uric acid (7.48 mg/dL

**Table 1.** Monitoring of BCR-ABL transcript during the follow up. The table shows the course of BCR-ABL transcript monitored by qRT-PCR.

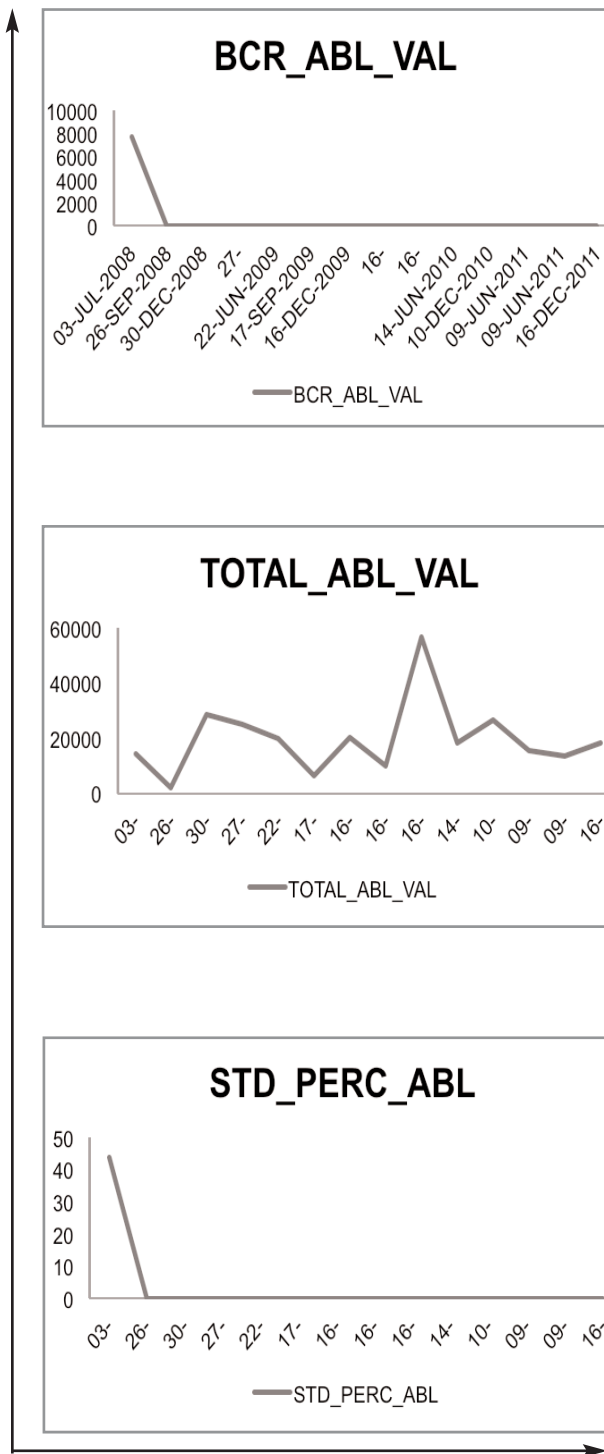
95 56257	03-JUL-2008	7758	14262	0,81	44,06
95 56257	26-SEP-2008	4	2239	0,81	0,14
95 56257	30-DEC-2008	37	28536	0,81	0,11
95 56257	27-MAR-2009	17	25047	0,81	0,05
95 56257	22-JUN-2009	5	19932	0,81	0,02
95 56257	17-SEP-2009	1	6273	0,81	0,01
95 56257	16-DEC-2009	4	20307	0,81	0,02
95 56257	16-MAR-2010	None Detected	10013	0,81	None Detected
95 56257	16-MAR-2010	5	56862	0,81	0,01
95 56257	14-JUN-2010	2	18468	0,81	0,01
95 56257	10-DEC-2010	1	26406	0,81	0
95 56257	09-JUN-2011	None Detected	15442	0,81	None Detected
95 56257	09-JUN-2011	None Detected	13618	0,81	None Detected
95 56257	16-DEC-2011	1	18394	0,81	0

[normal range: 2.4-5.7]) levels. LDH level was found to be upper than normal range (1245 U/L [normal range: 240-480]). On physical examination she was found to have hepatosplenomegaly.

The initial bone marrow biopsy in June 2008 revealed a hypercellular bone marrow with an increased ratio of myeloid elements and fibrosis. Philadelphia chromosome t(9;22) was positive in PCR analysis (t[9;22]/G6PDH= 0.3418), and also cytogenetical analysis was positive in all (20) metaphases for t(9;22)(q34;q11). So, she was diagnosed as chronic phase chronic myeloid leukemia. She was then randomised to dasatinib arm of the DASISION Study on 05.07.2008 at a dose of 1x100 mg/day peroral (po). After only 16 days of dasatinib treatment, she was accepted in complete hematologic remission. In 3rd. month visit, the patient was in hematologic and cytogenetic complete remission, and bone marrow was normocellular with no reticulin fiber increment. Complete cytogenetic response continued

during 6th., 12th., 18th., 24th. and 36th. months, respectively. During the follow-up, the patient was monitored by quantitative real-time PCR (qRT-PCR) (Table 1, Figure 1).

At 19th month of therapy, respiratory distress and grade 2 pleural effusion occurred under dasatinib. Dasatinib was stopped and diuretic treatment (spironolactone 1x25 mg/day, fluocortolone 1x20 mg/day peroral) was initiated. 16 days later, dasatinib 100 mg/day was started. At 26th month of therapy, the patient reported respiratory distress and thorax CT revealed a grade 2 pleural effusion. Dasatinib was stopped and diuretic treatment (spironolactone 1x25 mg/day, fluocortolone 1x40 mg/day peroral) was initiated. Dasatinib 1x100 mg/day was started 23 days later. Under diuretic treatment pleural effusion declined from grade 2 to grade 1, but dasatinib dose was reduced to 80 mg in 2011 January. And finally, at 29th. month, grade 3 pleural effusion occurred. Dasatinib was stopped, and diure-



**Figure 1.** BCR-ABL values of the CML patients during the administration of dasatinib

tics were started again. Two weeks later, dasatinib was started at a dose of 70 mg/day. The patients' last visit was on 2011 December. She had no respiratory distress, and was under dasatinib treatment at a dose of 70 mg/day. Pleural effusion was accepted as grade 2. Also the patient had some other non-serious adverse events (arthralgia, neuropathy, and dry eye) during the treatment period (Table 2).

## DISCUSSION

In this original research, we intended to assess the rational of managing CML and pleural effusion that successfully managed with dose reduction and supportive care. We observed that effective molecular monitoring and the proper management of pleural effusion during the first-line dasatinib administration in CML are essential. The representative patient with newly diagnosed chronic-phase CML has been treated with dasatinib, administered at a dose of 100 mg once daily. She was accepted in hematologic and cytogenetic complete remission at the early stage of the treatment. The DASISION study showed superior efficacy including significantly higher of complete cytogenetic response (83% vs 72%,  $p=0.001$ ) and major molecular response (46% vs 28%,  $p<0.0001$ ) and faster rates ( $p<0.0001$ ) for dasatinib 100 mg once daily ( $n=259$ ) compared with imatinib 400 mg once daily ( $n=260$ ) after 12-month follow up.<sup>11</sup> In the longer follow up, patients treated by dasatinib and imatinib achieved CCyR (86% vs 82%), MMR (64% vs 46%), CMR (17% vs 8%) and transformation to accelerated/ blastic phase CML (2.3% vs 5.0%), respectively.<sup>12</sup> S0325 trial showed similar results with DASISION that dasatinib has deeper molecular responses (3-log reductions in BCR-ABL transcript level) at 12 months compared with 400 mg of imatinib (59% vs. 43%) in patients with newly diagnosed CP-CML.<sup>13</sup> Overall, recent data showing superior efficacy of dasatinib versus imatinib in newly diagnosed CP-CML patients. In addition, NCCNv2.2012 panel recommends that second-generation TKIs may be an alternative treatment approach as a first-line therapy choice for all risk group of CML and especially for intermediate- to high-risk patients based on Sokal or Hasford score. Achievement of CCyR and/ or MMR within 12-month after the ini-

**Table 2.** Non-hematological and non-serious adverse effects during the follow-up

Adverse events	Seriousness	Onset Date	Resolution date	Grade	Relationship	Action
Arthralgia	Non-serious	05.07.2008	26.09.2008	2	Probable	None
Neuropathy	Non-serious	20.09.2009	...	1	Possible	None
Dry eye	Non-serious	20.09.2009	...	1	Possible	None, consulted to department of ophthalmology
Pleural effusion and respiratory distress	Serious	22.02.2010	09.03.2010	2	Certain	Drug was interrupted, diuretics were used
Pleural effusion and respiratory distress	Serious	17.11.2010	10.12.2010	2	Certain	Drug was interrupted, diuretics were used
Pleural effusion and respiratory distress	Serious	23.06.2011	...	3	Certain	Drug was interrupted, diuretics were used. Two weeks later, dasatinib was started (70 mg/day)

tiation of treatment was predictive of long-term treatment success regarding prolonged CCyR, very low risk of long-term progression, higher rate of OS, PFS, EFS and low risk for loss of CCyR.<sup>14-18</sup> Thus, achieving both a CCyR and MMR more quickly and at a higher rates should be an important treatment goal.

All grade of pleural effusion is frequent non-hematologic adverse event in dasatinib-treated patients.<sup>19</sup> Although pleural effusion risk in patients treated with 100 mg dasatinib once daily (14%) was lower than patients receiving 50 mg BID, 70 mg BID, and 140 mg once daily (23% to 26%) at 24-month follow up.<sup>7</sup> In addition, only 2% of patients treated with dasatinib 100 mg QD has been reported as grade 3 pleural effusion, with no grade 4 events, whereas grade 3 of 4 pleural effusion rates were 4% to 6% in other study arms. Rates at 24 months showed only a minimal increase compared with 12-month follow-up.<sup>7</sup> Rates at 60 months showed only a minimal increase compared with 24-month follow-up.<sup>8</sup> Recommendations for managing pleural effusion, are follows: after grade 2 AE, dasatinib is interrupted until the AE resolved, and then restarted at the original dose (100 mg QD); after recurrence of same grade 2 AE, dasatinib is interrupted and restarted at a reduced dose (80 mg QD); after second

recurrence of the same grade 2 AE, dasatinib discontinuation can be considered by the investigator according to the best interests of the patient; after grade 3&4 AE, dasatinib was interrupted until the AE resolved, and then restarted at a reduced dose; after recurrence of same grade 3&4 AE, dasatinib discontinuation can be considered. Pleural effusions can be also managed by treatment interruption, dose reduction and supportive therapy.<sup>20</sup> Porkka et al showed a possible correlation between pleural effusion and lymphocytosis and the achievement of cytogenetic response with dasatinib treatment.<sup>21</sup> In addition, patients with or without pleural effusion showed similar progression-free and overall survival, and cytogenetic response rates were higher in patients with a pleural effusion.<sup>21</sup> Other studies have presented that patients with lymphocytosis during dasatinib treatment achieved favorable response rate<sup>22,23</sup> and in parallel with this case report result.

In conclusion, pleural effusion may occur during dasatinib treatment and are generally grade II which can be easily managed by dose interruption, dose reduction, and supportive treatment such as diuretic/ steroids. Furthermore, serial molecular monitoring is the new standard of care in the management of CML.

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