Dasatinib-induced pleural effusion: Chylothorax, an option to consider

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Abstract:

Dasatinib is a drug for treatment of oncogene fusion protein BCR-ABL-positive chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia resistant/intolerant to imatinib. Pleural effusion (PE) is a common adverse effect, and in this context, we present four cases seen due to this cause. One of them is a chylothorax. The PE grade is variable, and the physiopathology is not well established, although a block in T-lymphocyte function or inhibition of platelet-derived growth factor receptor-β is suggested being involved. The PE is generally a lymphocyte-predominant exudate, but can also present as chylothorax. Several factors have been associated with its appearance, particularly the administration in two daily doses. Low grade (1–2) PEUs usually respond well to interrupt the treatment while those of higher grade may also require therapeutic thoracentesis and corticosteroids. There are currently no firm guidelines that establish when to resort to one form of treatment or another.

Key words:
Chylothorax, dasatinib, pleural effusion

Dasatinib was first used as second-line tyrosine-kinase inhibitor approved for treatment of oncogene fusion protein BCR-ABL-positive chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia resistant or intolerant to imatinib and, later, was considered as first-line therapy for patients with this pathology. Pleural effusion (PE) is a common complication during dasatinib therapy and the mechanism underlying the development of PE is currently unclear.

We present four patients with PE secondary to dasatinib, one a chylothorax, a little-reported finding. Although there have been numerous reports of dasatinib-related effusions, very few have provided complete pleural fluid analysis.

Case Report

Table 1 summarizes the clinical, radiological, and analytical characteristics of the four patients with PE due to dasatinib. They include two males and two females with ages between 50 and 71 years, diagnosed with chronic myeloid leukemia (three patients) and Philadelphia chromosome-positive acute lymphoblastic leukemia, in whom dasatinib was used as a first-line as well as a second-line drug (after imatinib; three patients). The dose was very variable (from 50 to 140 mg) and always administered in a single daily dose. The PE appeared within 2–60 months after starting the treatment, after having ruled out other causes of PE. The PE grades (according to the National Cancer Institute Common Terminology Criteria for adverse events, version 3.0) were from 1 to 3, with no accompanying pulmonary lesions or mediastinal masses in the chest computed tomography. The treatment ranged from the administration of diuretics (two patients) and oral corticosteroids (one case) to therapeutic thoracentesis (two patients), a decrease in the dose of the drug (in all of them) and finally stopping it in two cases. The response was a decrease in the PE in two patients and resolving it in the other two.

The PE was bilateral in two patients (although in Case 2 a thoracentesis was not performed on the left side due to there being a small amount of fluid), and on the right side, in the other two. Its appearance was lipemic in Case 1 (on both sides and with some blood staining) and serous in the other three. The biochemical characteristics were those of exudates, in accordance with the predominance of lymphocytes (80–87%). Very few patients have provided complete pleural fluid analysis.

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high triglyceride values were obtained on both sides in Case 1, which confirmed the diagnosis of a bilateral chylothorax. The values for cholesterol, adenosine deaminase, N-terminal fragment of pro-brain natriuretic peptide, glucose, interleukins, C-reactive protein, tumor markers, and tumor necrosis factor-α were nonspecific in all patients [Table 1]. The cytology and pleural fluid cultures were negative in all cases.

### Discussion

PE is a common complication during dasatinib therapy (incidence between 7% and 39%),[1-17] and the percentage and grades of PE are variable depending on the series that are reviewed. In those by Quintás-Cardama et al,[4] and Porkka et al,[15] the percentage of PE in Grades 1, 2, 3, and 4 were 27% and 16%, 25% and 65%, 40% and 16%, and 8% and 3%, respectively.

Various factors have been associated with the appearance of the PE. The prescription of a single dose (140 mg) per day is associated with a significantly lower number of PE than those who receive 70 mg twice a day (20% compared to 39%, P < 0.001), and a lower need to withdraw the drug.[14,16] In two studies, the dose of 100 mg once per day demonstrated that this dose was equally effective, but better tolerated as regards the incidence of PE reported (7% and 14%, respectively), than 50 mg twice a day (11% and 23%), 140 mg once a day (15% and 26%), and 70 mg twice a day (16% and 25%).[12,13] Wang et al. showed that the mean minimum concentration in the blood

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**Table 1: Clinical, radiological, and analytical characteristics of patients with pleural effusion due to dasatinib**

| Parameter                          | Case 1       | Case 2       | Case 3       | Case 4       |
|------------------------------------|--------------|--------------|--------------|--------------|
| Age (years)                        | 71           | 70           | 67           | 50           |
| Gender                             | Woman        | Man          | Woman        | Man          |
| Diagnosis                          | Ph+ ALL      | CML          | CML          | CML          |
| Treatment (first or second-line)   | Second-line  | First-line   | Second-line  | Second-line  |
| Dose (mg daily)                    | 140          | 100          | 50           | 100          |
| Time between start dasatinib and PE (months) | 2             | 9            | 60           | 43           |
| Grade PE                           | 2            | 2            | 3            | 1            |
| Pulmonary lesions (CT)             | No           | No           | No           | No           |
| Treatment PE                       | Dose reduction, CCS, diuretics and TT | Suspension and diuretics | Dasatinib suspension | Dose reduction and TT |
| Response                           | Decrease     | Resolution   | Resolution   | Decrease     |
| Laterality                         | Right        | Left         | Right        | Right        |
| Appearance                         | Hemorrhagic lipemic | Hemorrhagic lipemic | Serous       | Serous       |
| pH                                 | 7.43         | >7.80        | 7.43         | 7.43         | 7.43         |
| Total nucleated cell count (cells/µL) | 2260         | 2590         | 1700         | 4450         | 6620         |
| Polymorphonuclear cells (%)        | 12           | 14           | -            | -            | -            |
| Lymphocytes cells (%)              | 85           | 80           | 85           | 85           | 87           |
| Proteins (g/dL)                    | 4.2          | 4.1          | 3.5          | 6            | 4.9          |
| PF/S proteins ratio                | 0.63         | 0.61         | 0.51         | 0.66         | 0.67         |
| LDH (U/L)                          | 247          | 254          | 273          | 453          | 266          |
| PF/S LDH ratio                     | 0.67         | 0.59         | 0.65         | 1.08         | 0.89         |
| Triglycerides (mg/dL)              | 625          | 378          | -            | -            | -            |
| Cholesterol (mg/dL)                | 102          | 111          | 38           | 83           | 54           |
| Glucose (mg/dL)                    | 133          | 120          | 98           | 137          | 185          |
| IL-1 (pg/mL)                       | <5           | <5           | <5           | <5           | <5           |
| sIL-2R (U/mL)                      | 868          | 1231         | 1093         | 1255         | 727          |
| IL-6 (pg/mL)                       | 823          | 890          | 837          | 579          | 697          |
| IL-8 (pg/mL)                       | 35           | 53           | 28           | 43           | 23           |
| TNF-α (pg/mL)                      | 7.7          | 8.7          | 13.6         | 9.4          | 10.3         |
| CRP (mg/L)                         | 0.12         | 0.09         | 0.07         | 0.44         | 0.46         |
| CEA (ng/mL)                        | <0.5         | <0.5         | <0.5         | 1.2          | 2.6          |
| CA125 (U/L)                        | 340          | 556          | 271          | 303          | 255          |
| ADA (U/L)                          | 23           | 20           | 13           | 19           | 20           |
| NT-proBNP (pg/mL)                  | 160          | 164          | 138          | 121          | 69           |
| Cultive                            | Negative     | Negative     | Negative     | Negative     | Negative     |
| Cytology                           | Negative     | Negative     | Negative     | Negative     | Negative     |

ADA = Adenosine deaminase; CA‑125 = Cancer antigen 125; CCS = Corticosteroids; CEA = Carcinoembryonic antigen; CML = Chronic myeloid leukemia; CRP = C-reactive protein; IL‑1 = Interleukin‑1; IL‑6 = Interleukin‑6; IL‑8 = Interleukin‑8; LDH = Lactate dehydrogenase; NT‑proBNP = N-terminal fragment of pro-brain natriuretic peptide; PE = Pleural effusion; PF/S = Pleural fluid/serum; Ph+ ALL = Philadelphia chromosome positive acute lymphoblastic leukemia; sIL‑2R = Soluble interleukin‑2 receptors; TNF‑α = Tumor necrosis factor-alpha; TT = Therapeutic thoracentesis
of the patients with 100 mg dasatinib in a single daily dose was 2.69 ng/mL, and 6.9 ng/mL in those who took 70 mg twice a day.[14] Although both prescriptions achieve the same hematological and cytological responses, the highest mean concentration of those who took the drug twice a day could be the reason for the higher incidence of PE. All this suggests that the intermittent BCR-ABL inhibition by dasatinib may be sufficient to achieve the appropriate cytological effect, but with less adverse effects. Furthermore, the median time to the development of an effusion was 315 days for 100 mg once-daily group, compared to 289, 148, and 136 days, with 50 mg twice daily, 140 mg once daily, and 70 mg twice daily, respectively.[15] The incidence of PE with dasatinib in the major studies published up until now is summarized in Table 2. Porkka et al. evaluated the potential factors for developing a PE in those patients on treatment with dasatinib.[15] They found that age and lymphocytes increase the risk of a PE (patients ≥66 years have a higher risk than those aged between 46 and 66 years, and these, in turn, higher than those <46 years, and a lymphocyte count of >3.6 × 10^9/L on at least two occasions after 4 weeks of treatment with dasatinib).

Table 2: Pleural effusion associated with dasatinib

| Reference                  | Number of patients | Male (%) | Initial drug dose     | Incidence of effusion, n (%) | Laterality | Treatment                                                                 |
|----------------------------|--------------------|----------|-----------------------|------------------------------|-----------|---------------------------------------------------------------------------|
| Kantarjian et al.[1]       | 259                | 56       | 100 mg qd**           | 37 (14)                      | NR        | Interruption, thirty patients; dose reduction, 19; diuretics, 17; CCS, 17; TT, 4 |
| Talpaz et al.[2]           | 84                 | 47       | 15-240 mg daily       | 15 (18)                      | NR        | The pleural effusions were managed with diuretics, thoracentesis, or pleurodesis |
| Bergeron et al.[3]         | 40                 | NR       | 70 mg bid             | 6 (15)                       | 2/6 BLT   | Interruption, six patients (all with 70 mg bid): full resolution in 5 and partial in 1 |
|                           |                    |          |                       |                              |           | No reappearance in which reintroduced (three patients) Diuretics, three patients |
| Quintás-Cardama et al.[4]  | 138                | 50       | Varying dosis         | 48 (35)                      | 38/48 BLT | Interruption, forty patients (14 more than one occasion); dose reduction, 34; CCS, 7; Diuretics, 19 ; TT, 9; peritoneovenous shunt (Denver), 2 |
| Cortes et al.[5]           | 74                 | 55       | 70 mg bid             | 21 (28)                      | NR        | Pleural effusions were reversible with temporary dose interruption, diuretics, and, in some patients, pulse steroids |
|                           | 42                 | 52       |                       | 6 (14)                       |           | Most pleural effusions were uncomplicated, resolving with temporary dose interruption, diuretics, and, in some cases, pulse steroids; TT, three patients |
| Guilhot et al.[6]          | 107                | 51       | 70 mg bid             | 25 (23)                      | NR        | Pleural effusions were successfully managed with dasatinib dose interruption, diuretics, and/or pulse steroid therapy |
| Kantarjian et al.[7]       | 101                | 53       | 70 mg bid             | 17 (17)                      | NR        | Pleural effusions were successfully managed with dasatinib dose interruption, diuretics, and/or pulse steroid therapy |
| Ottmann et al.[8]          | 36                 | 23       | 70 mg bid             | 7 (19)                       | NR        | Pleural effusions were successfully managed with dasatinib dose interruption, diuretics, and/or pulse steroid therapy |
| Hochhaus et al.[9]         | 387                | 49       | 70 mg bid             | 106 (27)                     | NR        | Interruption, three patients CcS, 1 TT, 3 Pleurodesis, 1 |
| de Lavallade et al.[10]    | 3                  | NR       | 140 mg daily          | Overall 17 (27)              | 2/17 BLT  | Interruption, three patients CcS, 1 TT, 3 Pleurodesis, 1 |
|                           | 9                  |          | 50 mg bid             |                              |           | Pleurodesis, 1 |
|                           | 4                  |          | 100 mg daily          |                              |           | Pleurodesis, 1 |
|                           | 46                 |          | 70 mg bid             |                              |           | Pleurodesis, 1 |
| Cortes et al.[11]          | 157                | 56       | 70 mg bid             | 45 (29)                      | NR        | Most instances of pleural effusion were uncomplicated and resolved with temporary dose interruption, diuretics, and in some patients, with steroids |
| Shah et al.[12]            | 165                | 50       | 100 mg daily          | 12 (7)                       | NR        | Discontinuation of treatment in 2% of 100 mg/day arm and 4-5% in other arms |
|                           | 163                | 42       | 140 mg daily          | 24 (15)                      | NR        | Discontinuation of treatment in 2% of 100 mg/day arm and 4-5% in other arms |
|                           | 167                | 51       | 50 mg bid             | 19 (11)                      | NR        | Discontinuation of treatment in 2% of 100 mg/day arm and 4-5% in other arms |
|                           | 167                | 46       | 70 mg bid             | 26 (16)                      | NR        | Discontinuation of treatment in 2% of 100 mg/day arm and 4-5% in other arms |
| Apperley et al.[13]        | 174                | 55       | 70 mg bid             | 47 (27)                      | NR        | NR |
| Kantarjian et al.[14]      | 158                | 56       | 140 mg daily          | 31 (20)                      | NR        | Discontinuation of treatment in 4% of daily intake and 9% of twice daily |
|                           | 159                | 59       | 70 mg bid             | 62 (39)                      | NR        | Discontinuation of treatment in 4% of daily intake and 9% of twice daily |
| Porkka et al.[15]          | 165                | NR       | 100 mg daily          | 23 (14)                      | NR        | Interruption, 83 patients (12 with 100 mg, 25 with 70 mg, 24 with 140 mg and 22 with 50 mg) Reduction, 51 (8, 16, 13 14, respectively) Diuretics, 69 (13, 19, 17 years 20, respectively) CcS, 32 (6, 9, 8 years 9, respectively) |
|                           | 167                |          | 70 mg bid             | 42 (25)                      | NR        | Interruption, 83 patients (12 with 100 mg, 25 with 70 mg, 24 with 140 mg and 22 with 50 mg) Reduction, 51 (8, 16, 13 14, respectively) Diuretics, 69 (13, 19, 17 years 20, respectively) CcS, 32 (6, 9, 8 years 9, respectively) |
|                           | 163                |          | 140 mg daily          | 43 (26)                      | NR        | Interruption, 83 patients (12 with 100 mg, 25 with 70 mg, 24 with 140 mg and 22 with 50 mg) Reduction, 51 (8, 16, 13 14, respectively) Diuretics, 69 (13, 19, 17 years 20, respectively) CcS, 32 (6, 9, 8 years 9, respectively) |
|                           | 167                |          | 50 mg bid             | 39 (23)                      | NR        | Interruption, 83 patients (12 with 100 mg, 25 with 70 mg, 24 with 140 mg and 22 with 50 mg) Reduction, 51 (8, 16, 13 14, respectively) Diuretics, 69 (13, 19, 17 years 20, respectively) CcS, 32 (6, 9, 8 years 9, respectively) |
| Lilly et al.[16]           | 40                 | 45       | 140 mg daily          | 7 (18)                       | NR        | NR |
|                           | 44                 | 50       | 70 mg bid             | 14 (32)                      | NR        | NR |
| Saglio et al.[17]          | 107                | NR       | 140 mg daily          | 22 (21)                      | NR        | The once-daily arm had fewer dose reductions or interruptions because of toxicity compared with the twice-daily arm |
|                           | 102                |          | 70 mg bid             | 23 (26)                      | NR        | The once-daily arm had fewer dose reductions or interruptions because of toxicity compared with the twice-daily arm |

Bid = Twice daily; BLT = Bilateral; CCS = Corticosteroids; NR = Not reported; qd = Every day; TT = Therapeutic thoracentesis. **Dose escalation to 140 mg qd was allowed for suboptimal response. *Modification of the dasatinib dose was allowed after 4 weeks of treatment (escalation; reduced; or interrupted)
Two independent studies found that increased blood pressure, previous cardiac history, and to administer dasatinib twice daily, are also associated with a higher risk of PE.[4,10] Furthermore, in the study by de Lavallade et al.[10] a history of autoimmune disease (relative risk [RR] 4.3, 95% confidence interval [95% CI]; 1.3–14; \( P = 0.001 \)), a skin rash with dasatinib (RR 5.3, 95% CI; 1.9–14.6, \( P = 0.001 \)), and hypercholesterolemia (RR 3.5, 95% CI; 1.8–14.6, \( P = 0.037 \)) were also associated with a higher risk of PE. That the majority was exudates, suggest that the PE was neither related to fluid retention nor that it was due to kidney or cardiac failure. The predominance of lymphocytes seen in the majority of cases could indicate the mediation of an immunological mechanism. The suggested mechanisms of action are a block in T-lymphocyte function at clinically relevant concentrations, including their proliferation, activation, and cytokine production, or by the inhibition of platelet-derived growth factor receptor-β (PDGFR-β) expressed in pericytes that intervene in angio-lymphangiogenesis.[22] A deficiency of PDGFR-β in human lymphedema distichiasis is associated with the formation of abnormal initial lymphatics while others propose that PDGF-BB and its receptor, PDGFR-β, are directly lymphangiogenic.[23] A possible relationship to the pathogenesis of yellow nail syndrome has also been suggested.[19]

The pleural fluid analysis usually shows an exudate with a predominance of lymphocytes, and usually bilateral, with no other relevant characteristics. However, cases of exudates with a predominance of neutrophils[18] have also been described, as well as transudates[18] and chylothorax.[18,19]

The management of these PE includes stopping or reducing the dose of dasatinib in symptomatic patients (Grades 2–4)[11] and to administer diuretics or a short course of corticosteroids, with variable results. Table 2 provides a summary of the treatments used in the most important series.[1–17] There are no firm guidelines that establish when to resort to one form of treatment or another, although Brixey and Light propose some recommendations in this regard.[28]

In summary, dasatinib is a drug that is used for the treatment of refractory chronic myeloid leukemia and acute lymphoblastic leukemia. PE is a common adverse effect, and the mechanism by which it is developed is not well established. The pleural fluid is generally an exudate with a predominance of lymphocytes, but can also present as a chylothorax. The incidence decreases when a single daily dose is administered. The low-grade effusions usually respond well to the stopping of the treatment while the higher grades also require therapeutic thoracentesis and corticosteroids. On looking at these data in patients on treatment with dasatinib that present with a chylothorax, the possibility that this may be due to taking the drug should be taken into account. As dasatinib is most often used once daily in patients who have any of these two diseases, further studies are needed to try and determine the mechanism by which this drug can induce a chylothorax.

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Conflicts of interest
There are no conflicts of interest.

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