Case Report

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

Lucía Ferreiro[1,2], Esther San-José[2,3], Juan Suárez-Antelo[1], Luis Valdés[1,2]

Departments of [1]Pulmonology and [3]Clinical Analysis, University Clinical Hospital of Santiago de Compostela, [2]Interdisciplinary Research Group in Pulmonology, Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, A Coruña, Spain

Address for correspondence:
Dr. Lucía Ferreiro, Department of Pulmonology, University Clinical Hospital of Santiago de Compostela, Travesía A Choupana s/n, 15702 Santiago de Compostela, A Coruña, Spain.
E-mail: lferfer7@gmail.com

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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) PEs 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.[1] Pleural effusion (PE) is a common complication during dasatinib therapy,[1-17] 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.[4,18,19] Although there have been numerous reports of dasatinib-related effusions, very few have provided complete pleural fluid analysis.

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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)[20] 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

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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 (imatinib previous)		First-line	Second-line (imatinib previous)	Second-line (imatinib previous)
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	Right
Appearance	Hemorrhagic lipemic	Hemorrhagic lipemic	Serous	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

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%).[12,15] Wang *et al*. showed that the mean minimum concentration in the blood

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.[21] 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 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, 15; 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)		
Guilhot *et al*.[6]	107	51	70 mg bid	25 (23)	NR	Most pleural effusions were uncomplicated, resolving with temporary dose interruption, diuretics, and, in some cases, pulse steroids; TT, three patients
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	NR
Hochhaus *et al*.[9]	387	49	70 mg bid	106 (27)	NR	NR
de Lavallade *et al*.[10]	3	NR	140 mg daily	Overall 17 (27)	2/17 BLT	Interruption, three patients
	9		50 mg bid			CCS, 1
	4		100 mg daily			TT, 3
	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/or 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)		
	167	51	50 mg bid	19 (11)		
	167	46	70 mg bid	26 (16)		
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)		
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)
	167		70 mg bid	42 (25)		
	163		140 mg daily	43 (26)		Reduction, 51 (8, 16, 13 14, respectively)
	167		50 mg bid	39 (23)		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)		
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)		

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.[18]

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[3] have also been described, as well as transudates[4] and chylothorax.[4,18,19]

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.[20]

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.

References

1. Kantarjian HM, Shah NP, Cortes JE, Baccarani M, Agarwal MB, Undurraga MS, *et al.* Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). Blood 2012;119:1123-9.
2. Talpaz M, Shah NP, Kantarjian H, Donato N, Nicoll J, Paquette R, *et al.* Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. N Engl J Med 2006;354:2531-41.
3. Bergeron A, Réa D, Levy V, Picard C, Meignin V, Tamburini J, *et al.* Lung abnormalities after dasatinib treatment for chronic myeloid leukemia: A case series. Am J Respir Crit Care Med 2007;176:814-8.
4. Quintás-Cardama A, Kantarjian H, O'brien S, Borthakur G, Bruzzi J, Munden R, *et al.* Pleural effusion in patients with chronic myelogenous leukemia treated with dasatinib after imatinib failure. J Clin Oncol 2007;25:3908-14.
5. Cortes J, Rousselot P, Kim DW, Ritchie E, Hamerschlak N, Coutre S, *et al.* Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis. Blood 2007;109:3207-13.
6. Guilhot F, Apperley J, Kim DW, Bullorsky EO, Baccarani M, Roboz GJ, *et al.* Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase. Blood 2007;109:4143-50.
7. Kantarjian H, Pasquini R, Hamerschlak N, Rousselot P, Holowiecki J, Jootar S, *et al.* Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia after failure of first-line imatinib: A randomized phase 2 trial. Blood 2007;109:5143-50.
8. Ottmann O, Dombret H, Martinelli G, Simonsson B, Guilhot F, Larson RA, *et al.* Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: Interim results of a phase 2 study. Blood 2007;110:2309-15.
9. Hochhaus A, Baccarani M, Deininger M, Apperley JF, Lipton JH, Goldberg SL, *et al.* Dasatinib induces durable cytogenetic responses in patients with chronic myelogenous leukemia in chronic phase with resistance or intolerance to imatinib. Leukemia 2008;22:1200-6.
10. de Lavallade H, Punnialingam S, Milojkovic D, Bua M, Khorashad JS, Gabriel IH, *et al.* Pleural effusions in patients with chronic myeloid leukaemia treated with dasatinib may have an immune-mediated pathogenesis. Br J Haematol 2008;141:745-7.
11. Cortes J, Kim DW, Raffoux E, Martinelli G, Ritchie E, Roy L, *et al.* Efficacy and safety of dasatinib in imatinib-resistant or -intolerant patients with chronic myeloid leukemia in blast phase. Leukemia 2008;22:2176-83.
12. Shah NP, Kantarjian HM, Kim DW, Réa D, Dorlhiac-Llacer PE, Milone JH, *et al.* Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. J Clin Oncol 2008;26:3204-12.
13. Apperley JF, Cortes JE, Kim DW, Roy L, Roboz GJ, Rosti G, *et al.* Dasatinib in the treatment of chronic myeloid leukemia in accelerated phase after imatinib failure: The START a trial. J Clin Oncol 2009;27:3472-9.
14. Kantarjian H, Cortes J, Kim DW, Dorlhiac-Llacer P, Pasquini R, DiPersio J, *et al.* Phase 3 study of dasatinib 140 mg once daily versus 70 mg twice daily in patients with chronic myeloid leukemia in accelerated phase resistant or intolerant to imatinib: 15-month median follow-up. Blood 2009;113:6322-9.
15. Porkka K, Khoury HJ, Paquette RL, Matloub Y, Sinha R, Cortes JE. Dasatinib 100 mg once daily minimizes the occurrence of pleural effusion in patients with chronic myeloid leukemia in chronic

phase and efficacy is unaffected in patients who develop pleural effusion. Cancer 2010;116:377-86.
16. Lilly MB, Ottmann OG, Shah NP, Larson RA, Reiffers JJ, Ehninger G, *et al*. Dasatinib 140 mg once daily versus 70 mg twice daily in patients with Ph-positive acute lymphoblastic leukemia who failed imatinib: Results from a phase 3 study. Am J Hematol 2010;85:164-70.
17. Saglio G, Hochhaus A, Goh YT, Masszi T, Pasquini R, Maloisel F, *et al*. Dasatinib in imatinib-resistant or imatinib-intolerant chronic myeloid leukemia in blast phase after 2 years of follow-up in a phase 3 study: Efficacy and tolerability of 140 milligrams once daily and 70 milligrams twice daily. Cancer 2010;116:3852-61.
18. Goldblatt M, Huggins JT, Doelken P, Gurung P, Sahn SA. Dasatinib-induced pleural effusions: A lymphatic network disorder? Am J Med Sci 2009;338:414-7.
19. Huang YM, Wang CH, Huang JS, Yeh KY, Lai CH, Wu TH, *et al*. Dasatinib-related chylothorax. Turk J Haematol 2015;32:68-72.
20. Brixey AG, Light RW. Pleural effusions due to dasatinib. Curr Opin Pulm Med 2010;16:351-6.
21. Wang X, Hochhaus A, Kantarjian HM, Agrawal S, Roy A, Pfister M, *et al*. Dasatinib pharmacokinetics and exposure-response (E-R): Relationship to safety and efficacy in patients (pts) with chronic myeloid leukemia (CML). J Clin Oncol 2008;26 (15 Suppl):3590.
22. Sie M, den Dunnen WF, Lourens HJ, Meeuwsen-de Boer TG, Scherpen FJ, Zomerman WW, *et al*. Growth-factor-driven rescue to receptor tyrosine kinase (RTK) inhibitors through Akt and Erk phosphorylation in pediatric low grade astrocytoma and ependymoma. PLoS One 2015;10:e0122555.
23. Cao R, Björndahl MA, Religa P, Clasper S, Garvin S, Galter D, *et al*. PDGF-BB induces intratumoral lymphangiogenesis and promotes lymphatic metastasis. Cancer Cell 2004;6:333-45.