Dasatinib-induced pleural and pericardial effusion: A case report and review

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**Abstract**

**Introduction**: Tyrosine Kinase Inhibitors (TKI) have dramatically changed the prognostic of chronic myeloid leukemia. However, they have been associated with several side effects.

**Case report**: We describe a case of a patient admitted for bilateral exudative pleural and pericardial effusions. After a complete work-up, we concluded to a dasatinib-related side effect.

**Management and outcome**: The patient received oxygen supply, aerosols of ipratropium/salbutamol, and 50 mg of Prednisone for 5 days. The treatment by dasatinib was stopped. She remained asymptomatic at the two-month control by her haematologist. The chest x-ray showed a small remaining bilateral effusion.

**Discussion**: Based on this case, we performed a literature review on the subject to give insight on the associated risk factors, treatment options and prognosis. Dasatinib-related pleural effusion is frequent, but most often asymptomatic. Further studies are needed to better understand its mechanism and help guide treatment.

**Keywords**: Dasatinib; pleural; pericadial; effusion; side effect; case report.

**Introduction**

Chronic Myeloid Leukaemia (CML) is a myeloproliferative disorder of the hematopoietic stem cell caused by a translocation between the BCR and ABL gene. The resulting Philadelphia chromosome (t9; 22) promotes unregulated proliferation of myeloid precursor cells. The incidence of CML is 1-1.5/100’000 per year. Tyrosine Kinase Inhibitors (TKI) have dramatically changed prognostic and treatment of the disease. First generation TKI may result in the development of resistance and intolerance. Amongst second generation TKI, dasatinib is generally well tolerated. However, it has been associated with a higher risk for Pleural Effusions (PE). In this article, we describe a case of bilateral dasatinib-induced pleural and pericardial effusion, summarize available evidence on this condition and propose a management strategy.

**Case description**

A 59 years old woman known for type 2 diabetes, tobacco related chronic obstructive pulmonary disease and CML, presented to ED for a one-day history of dyspnea at rest, cough and sputum expectoration. She also complained of an interscapular pain. She had no fever, night sweet, weight loss or history of travelling. Her only medication consisted of dasatinib 100 mg daily. At the diagnosis of CML (2016), she started imatinib 400 mg that resulted in major molecular response. However, the treatment had to be discontinued after 8 months because of a facial oedema (very common side effect of imatinib). Then, her medication switched with dasatinib for the last 2.5 years.

On admission, the patient was tachypneic (20 breaths/min), tachycard (110 beats/min), her blood pressure was 127/82
mmHg, her temperature 37.1°C and oxygen saturation was 85% on room air. Pulmonary auscultation revealed wheezing and bibasal hypoventilation. There was no leg oedema or hepatosplenic reflex. The cardiac examination was unremarkable. We excluded enlarge liver, spleen, or lymph nodes.

The laboratory showed a leucocytosis (13.2 G/l) and a moderately elevated C-reactive protein (31 mg/l), but no renal or hepatic dysfunction and an unraised NT-proBNP (90 ng/l). The chest CT-scan confirmed the bilateral pleural effusion and a 1 cm large pericardial effusion. The transthoracic echocardiography revealed no sign of compression and a normal ventricular function. Thoracocentesis retrieved 1.5 liters of an exudative pleural liquid (2 /3 Light’s criteria: Pleural LDH=181 U/l, plasma LDH=181 U/l (ratio>0.6), pleural protein=47 g/l, plasma protein=71 g/l (ratio>0.5)). The liquid was predominantly lymphocytic (6170 cells, 97% of lymphocytes, 3% of polymorpho-nucleated cells). The analysis showed a negative adenosine deaminase assay, no bacterial growth, no malignant cells on cytology, and no argument for a chylothorax. The BCR-ABL was undetectable (major molecular response).

We concluded to a dasatinib-induced bilateral pleural and pericardial effusion. The final Naranjo score is then calculated at 7 points, making the adverse drug reaction probable. Thus, the patient received oxygen supply, aerosols of ipratropium/salbutamol, and 50 mg of Prednisone for 5 days. The treatment by dasatinib was stopped. The clinical evolution was good after the thoracentesis, without any further needs of oxygen supply or new thoracentesis. The patient could leave the hospital after 3 days.

She remained asymptomatic at the two-month control by her haematologist. The chest x-ray showed a small remaining bilateral effusion. In the end, nilotinib treatment never started, because BCR-ABL was still undetectable. Instead, it was decided to monitor her BCR-ABL transcript levels.

Discussion

TKI have changed the prognostic of CML but have also been associated to several important side effects. The case illustrates a bilateral pleural and pericardial effusion under dasatinib. To collect information on prevalence, risk factors, treatment strategy and prognosis, we performed a literature search in Medline using the keywords (((dasatinib)[Title] AND pleural effusion [Title])). We retrieved 15 relevant article out of 24, mostly case series/reports (n=6), and phase III trial (n=3). Overall, the available evidence included 623 PE in 2397 patients (Table 1).

Prevalence and associated factors

In two phase 3 trials that evaluated patients with CML and Philadelphia chromosome-positive acute lymphoblastic leukaemia treated with dasatinib (the DASISION and the 034/Dose-optimization study), the drug-induced PE was found in 28% and 33% of patients [1,2]. PE prevalence could range between 22% [3] to as high as 69% [4], depending on the population studied, age, drug dosage, and length of follow-up. PE can occur any time after the introduction of dasatinib [Table 1], but the risk increases with the duration of the treatment [2,5]. In DASISION study, the annual incidence of 8% was steady over time [2]. PE is bilateral in two third [6] to three quarter [7] of cases. Associated cardiac effusion is found in 8 to 29% of cases [7,8].

The main risks factors commonly accepted to develop PE under dasatinib are: Age over 65 years [1], duration of the treatment, and the daily dose of dasatinib. There are also other risk factors that have been identified by authors (detailed in Table 1). Daily dose of 140 mg or higher compared to 100 mg or less are associated with an increased risk of PE (Figure 1). The standard daily dose acceptable for the chronic phase is 100 mg once daily, but higher dose (140 mg) can be given during the accelerated or blastic phase [1]. In addition, if dasatinib is taken twice daily (regardless of the dose), it seems to increase the risk to develop a PE [9,10]. Finally, lymphocytosis seems to be a risk factor for the development of PE but it is also associated with good response to treatment [11]. The risk of PE exists with most of the TKIs currently approved for both first and second line CML-CP (chronic myeloid leukaemia in chronic phase) treatment, but is much higher with dasatinib [12]. Further studies are needed to determine the exact mechanism of PE in human and understand the difference in TKI risk.

The mechanism of “Primary” PE remains unclear. A recent animal study suggests that dasatinib alters endothelial barrier integrity, which result in increased pulmonary vascular endothelial permeability, eventually leading to PE [13]. Other studies pointed an immune-mediated mechanism, since the pleural liquid is an exudate containing high lymphocyte counts and that pericardial effusion is associated to PE in 26% of patients (Table 1) [14]. In the DASISION trial, pleural effusion developed more often in patients with lymphocytosis (like in our case), although this difference was not statistically significant (1). Mustjoki et al. suggested that dasatinib, through TK inhibition, may induce a reversible state of aberrant autoimmune reactivity with anti-leukemic and anti-host effect [15]. This is consistent with an early and deep molecular response of patients with PE compared to the rest of the cohort [16]. Beside “Primary” dasatinib-induced PE, which is by far the most frequent, dasatinib can be associated with “Secondary” PE through drug related heart failure, nephrotic syndrome, increased risk of pulmonary embolism and infection.

Treatment and prognosis

There is no consensus on the management of dasatinib-induced PE. Specialized centres manage it with a great heterogeneity [16]. We propose here (Figure 1) a pragmatic strategy, based on published evidence.

In the first step, workup of PE should look for a congestive heart failure, sign of infection, presence of thromboembolic disease, or other dasatinib unrelated PE aetiology. If there is no obvious alternative diagnosis, the patient is asymptomatic and the size of the effusion is small (Figure 1), a simple follow up by a chest x-ray could be appropriate. Nevertheless, PE that persists or is suggestive of an alternative diagnosis, deserve diagnostic thoracocentesis. If the effusion is moderate, and/or symptomatic, dasatinib should be temporarily stopped until PE resolution, and then rechallenged at a lower dose. Maintenance of the same doses, doses reduction and treatment holiday has been associated respectively with a 100%, 60%, and 75% recurrence of PE in an observational study [16]. There is a minimal impact on patient survival or response rate with a temporary drug cessation or a diminution of the daily dose [16]. Drug dos-
age alteration (50 mg) or cessation can be directed by plasma drug concentration [17]. In one small study, dose reduction (50 mg) was associated with an effective PE management and disease control [17]. Drug monitoring could also play a role in PE prevention and choice of the lower effective drug dosage [17]. In a randomized study, patients with a high \( [C]_{\text{min}} \) had dasatinib dose reduced (by 20 mg every 2 weeks to a minimum dosage of 40 mg/day) to obtain a plasma \( [C]_{\text{min}} \) of < 3/nmol/L. Patients randomized with this strategy had lower risk of PE at 3 years (11% versus 45%) but also less drug discontinuation (13% versus 27%) compared to the control group with equivalent disease control [17].

When a thoracentesis is performed, the fluid analysis is usually exudative and contains high lymphocyte count. Diuretic and corticoid have frequently been given, but their efficacy is proven in this context. Despite this, in the case of transudative PE, diuretic should be considered. For exudative PE and persistent/recurrent PE despite other measure, corticoid trials remains a possible option. A recent study has shown that a treatment by tolvaptan, an orally vasopression V2-receptor antagonist, may be useful [18]. Despite an adequate management with dose reduction, recurrent drug-related PE occurred in around 60% of the cases [1,12]. Nilotinib treatment should be considered when the above measures are ineffective or when the PE is recurrent [4,5,9,11,19].

PE has no impact on disease specific survival, since 96% of these patients achieve a complete cytogenic remission and 82% achieve a major molecular response (BCR-ABL1 <0.1%, main goal of the treatment of chronic myeloid leukaemia) [2].

**Figure 1:** Possible strategy for management of dasatinib related pleural effusion.

**Conclusion**

Dasatinib is an effective and generally well-tolerated second generation TKI for the treatment of CML. Dasatinib-induced pleural effusion is a frequent (and frequently overlooked) complication of the treatment. Mechanisms related to its development and treatment modalities deserve to be further explored. When a large or symptomatic pleural effusion occurs, temporal treatment alteration is safe. In case of recurrent effusion, treatment switch to nilotinib should be considered.

**Conflict of interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**References**


<table>
<thead>
<tr>
<th>Auto (year, country)</th>
<th>Pleural effusion (PE)</th>
<th>Pericardial effusion</th>
<th>Risk factor identified by the author</th>
<th>Dasatinib</th>
<th>Thoracocentesis</th>
<th>Clinical Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matile (2020), Switzerland</td>
<td>1 (-)</td>
<td>L + R</td>
<td>-</td>
<td>Time to PE 2.5 y</td>
<td>Daily dose 100mg</td>
<td>n/PE 1</td>
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<tr>
<td>Nakaya (20) (2018), Japan</td>
<td>8/22 (36%)</td>
<td>NA</td>
<td>-</td>
<td>Age (&gt;65 : 7/8) (Median age with PE : 66 yo vs 42 yo without PE)</td>
<td>Time to PE 5-26w</td>
<td>Daily dose 100mg</td>
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<tr>
<td>Porkka (3) (2009), Finland</td>
<td>147/66.2 (22%)</td>
<td>NA</td>
<td>-</td>
<td>Age (&gt;60 : 93/256 = 36%) (&lt;60 : 54/406 = 13%)</td>
<td>Time to PE 315 d</td>
<td>Daily dose 100mg</td>
</tr>
<tr>
<td>Cortes (2) (2016), USA</td>
<td>73/258 (28%)</td>
<td>NA</td>
<td>-</td>
<td>Age (&gt;65: 15/25 = 60%) (&lt;65: 58/233 = 25%)</td>
<td>Time to PE 2.5 y</td>
<td>Daily dose -</td>
</tr>
<tr>
<td>Latagliata (14) (2012), Italy</td>
<td>52/172 (30%)</td>
<td>NA</td>
<td>14/172 (8%)</td>
<td>Concomitant pulmonary disease</td>
<td>Daily dose (All the patient in the study were &gt;60yo)</td>
<td>Time to PE 20 month</td>
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<td>Kim (10) (2011), Korea</td>
<td>35/65 (54%)</td>
<td>13 (37%) unilateral 22 (63%) L + R</td>
<td>Disease phase Dose schedule [twice daily, Daily dose]</td>
<td>Time to PE 11 month</td>
<td>Daily dose Variable</td>
<td>PE/n (%): 35/65 (54%)</td>
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<td>Krauth (4) (2011), Austria</td>
<td>9/13 (69%)</td>
<td>NA</td>
<td>2/13 (15%)*</td>
<td>Several factor and comorbidties (not described)</td>
<td>Daily dose 100mg daily (5/9 with IP) 140mg daily (4/4 with IP)</td>
<td>PE/n (%): 9/13 (69%)</td>
</tr>
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<td>Hughes (1) (2019), Australia</td>
<td>- 73/258 (28%) - 220/670 (33%)</td>
<td>NA</td>
<td>-</td>
<td>Duration of treatment Age (DASISON : 41y without PE, 36y with PE)</td>
<td>Daily dose 100mg</td>
<td>PE/n (%): 147/66.2 (22%)</td>
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<td>Masal (11) (2019), Turkey</td>
<td>1 (100%)</td>
<td>L + R</td>
<td>1</td>
<td>-</td>
<td>Daily dose 100mg daily</td>
<td>PE/n (%): 1 (100%)</td>
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<td>Iurlo (12) (2017), Italy</td>
<td>198/853 (23%)</td>
<td>NA</td>
<td>34/196 (17.3 %)</td>
<td>Age median (at diagnostic: 60 yo)</td>
<td>Daily dose 100mg</td>
<td>PE/n (%): 198/853 (23%)</td>
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<td>Quinta’s-Carcarda (9) (2007), USA</td>
<td>48/138 (35%)</td>
<td>L + R in 79% of the cases</td>
<td>Cardiac disease Hypertension</td>
<td>Daily dose Twice-daily doses schedule</td>
<td>Time to PE 5 weeks</td>
<td>Daily dose &gt;140mg daily (n=4) 140 mg daily (n=35) 100mg daily (n=6) &lt;100mg daily (n=3)</td>
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<td>Mizuta (17) (2018), Japan</td>
<td>8/32 (25%)</td>
<td>NA</td>
<td>-</td>
<td>Age (but no statistical significance)</td>
<td>Daily dose 100mg</td>
<td>PE/n (%): 8/32 (25%)</td>
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