Lung Abnormalities after Dasatinib Treatment for Chronic Myeloid Leukemia
A Case Series

Anne Bergeron1, Delphine Réa2,3, Vincent Levy2, Clément Picard4, Véronique Meignin4, Jérôme Tamburini1, Heriberto Bruzzone-Giovanelli2, Fabien Calvo2, Abdellatif Tazi1, and Philippe Rousselot2

1Université Denis Diderot–Paris 7, Assistance Publique-Hôpitaux de Paris, Service de Pneumologie, Hôpital Saint-Louis, Paris, France; 2INSERM CIC 9504, Centre d’Investigations Cliniques, Paris, France; 3Université Denis Diderot–Paris 7, Assistance Publique-Hôpitaux de Paris, Service de Pneumologie, Hôpital Saint-Louis, Paris, France; 4Université Denis Diderot–Paris 7, Assistance Publique-Hôpitaux de Paris, Service de Pathologie, Hôpital Saint-Louis, Paris, France; and 5Université de Versailles Saint-Quentin en Yvelines, Service d’Hématologie Hôpital Mignot, Le Chesnay, France

Tyrosine kinase inhibitors have revolutionized the treatment of chronic myeloid leukemia and are increasingly used for other indications. Fluid retention, however, including pleural effusions, are a significant side effect of imatinib, the first-line treatment for chronic myeloid leukemia. We investigated pleural and pulmonary complications in patients treated with dasatinib, a novel multitargeted tyrosine kinase inhibitor, as part of clinical trial protocols. Of 40 patients who received dasatinib (70 mg twice daily) for imatinib resistance or intolerance, 9 (22.5%) developed dyspnea, cough, and chest pain. Of these nine patients, six had pleural effusions (all were exudates) and seven had lung parenchyma changes with either ground-glass or alveolar opacities and septal thickening (four patients had both pleural effusions and lung parenchyma changes). Lymphocytic accumulations were detected in pleural and bronchoalveolar lavage fluids in all patients except for one who presented with neutrophilic alveolitis. Pleural biopsies revealed lymphocytic infiltration in one patient and myeloid infiltration in another. After dasatinib interruption, lung manifestations resolved in all cases and did not recur in three of four patients when dasatinib was reintroduced at a lower dose (40 mg twice daily). Thus, lung physicians should be aware that lung manifestations, presumably related to an immune-mediated mechanism rather than fluid retention, may occur with dasatinib treatment.

Keywords: pleural effusion; tyrosine kinase inhibition

Tyrosine kinase inhibitors have revolutionized the treatment of chronic myeloid leukemia (CML) and are also increasingly used for other indications. Imatinib, which currently constitutes the first-line treatment for CML, is frequently associated with fluid retention, including pleural effusions. Dasatinib (Sprycel, formerly BMS-354825; Bristol-Myers Squibb, New York, NY) is a novel tyrosine kinase inhibitor of BCR-ABL (breakpoint cluster region-Abelson), SRC (v-src sarcoma viral oncogene homolog)-family kinases (including SRC, LCK [lymphocyte specific protein tyrosine kinase], LYN [v-yes Yamaguchi viral related oncogene homolog], and YES [Yamaguchi Sarcoma viral oncogene homolog 1]), PDGFR (platelet-derived growth factor receptor)-β, and c-KIT (proto-oncogene protein tyrosine kinase kit) (1, 2). Recently, dasatinib was shown to induce hematologic, cytogenetic, and molecular responses in patients with CML or Philadelphia chromosome–positive acute lymphoblastic leukemia who are resistant or intolerant to other tyrosine kinase inhibitors, such as imatinib or nilotinib (3–8). Although dasatinib is generally well tolerated, dasatinib-associated pleural effusions and dyspnea have been noted in clinical trials and are usually managed as a manifestation of fluid retention. However, a detailed description of these adverse events has not been published. Here, we describe 9 of 40 patients who developed dasatinib-associated lung abnormalities at our institution, show that these probably resulted from an immune-mediated mechanism rather than fluid retention, and report their management and outcome. Some of the results in this study have been previously presented in the form of an abstract (9).

METHODS

Between January 2005 and March 2006, 40 patients with chronic-phase CML received dasatinib after primary or secondary imatinib resistance (n = 29) or imatinib intolerance (n = 11) at Hôpital Saint-Louis in Paris, France (protocols CA180013, CA180017, CA180034). Twenty-seven patients received dasatinib 140 mg/day (3 received 140 mg daily, 24 received 70 mg twice daily) and 13 received dasatinib 100 mg/day (6 received 100 mg daily, 7 received 50 mg twice daily).

Chest X-rays and high-resolution computed tomography (HRCT) were performed in all patients who developed respiratory symptoms. Pleural fluids, obtained by thoracocentesis, were examined for total and differential cell counts, protein, and lactate dehydrogenase values. Surgical pleural biopsies were performed in two patients using video thoracoscopy, and one patient underwent a blind pleural biopsy. In patients with lung parenchyma abnormalities, bronchoscopy was performed and bronchoalveolar lavage (BAL) fluids were examined for cellular content. One patient underwent transbronchial biopsies. Pleural effusion and BAL fluids were extensively tested for infectious agents.

To investigate possible pulmonary emboli, pulmonary computed tomography (CT) angiography, ventilation–perfusion lung scans, and venous ultrasonography were performed. To evaluate left ventricular function, echocardiography, scintigraphy, cardiac CT, and blood N-terminal pro–brain natriuretic peptide (NT pro-BNP) measurements were performed.

RESULTS

Clinical Features

Of 40 patients who received dasatinib, 9 (22.5%) developed lung abnormalities presumably related to dasatinib (Table 1).
Median time between dasatinib treatment initiation and respiratory symptoms was 229 days (range, 20–510 d). Eight patients received dasatinib 70 mg twice daily throughout the treatment period, whereas patient 9 received 50 mg twice daily for 7 months followed by 70 mg twice daily for 4 months. Three of the nine patients had received dasatinib after imatinib intolerance, which was lung related in two cases (constrictive bronchiolitis in patient 2, which had partially resolved before dasatinib therapy, and hypersensitivity pneumonitis in patient 4, which had fully resolved). Six of the nine patients received dasatinib after primary or secondary imatinib resistance.

Chest X-rays and HRCT revealed moderate pleural effusions in six patients (two bilateral, four unilateral) and parenchymal changes in seven patients (including four with effusions) (Figure 1 and Table 2). No patient experienced peripheral edema after dasatinib treatment. When lung abnormalities were first detected, all nine patients were in complete hematologic remission, including three patients with a complete cytogenetic response.

Investigations
In the nine patients with lung abnormalities, mean white blood count was $9.1 \times 10^9/L$ (range, 2.5–23.1 $\times 10^9/L$), mean hemoglobin was 11.3 g/dl (range, 8.6–13.1 g/dl), mean platelet count was $226 \times 10^9/L$ (range, 47–895 $\times 10^9/L$), and peripheral oxygen saturations were greater than 95%.

Protein content analysis revealed pleural effusion fluids to be blood-free exudates in all six cases. Fluid cytologic analyses identified lymphocytes in five patients (61 ± 33%) and neutrophils in the sixth, with no pathogens detected. Surgical pleural biopsies revealed a marked pleural lymphocytic or myeloid infiltration in separate patients (Table 2).

BAL fluid analysis, performed in five patients, revealed a median cell count of $714 \pm 694 \times 10^3$ cells/ml, with an increased lymphocyte percentage in four patients (53.5 ± 31.8%), an increased neutrophil percentage (36%) in one patient, and no eosinophils. Hemosiderin-laden macrophages (20–95%) were detected in all but one case (patient 2). All BAL specimens were pathogen negative, except for bronchial colonization by Klebsiella oxytoca in patient 7.

Tests were performed to rule out pulmonary embolism or abnormal left ventricular function. No abnormalities were detected.

Management and Outcome
Dasatinib treatment was interrupted in eight patients, either immediately after diagnosis of lung involvement (five patients), or after a course of diuretics (three patients), which were ineffective (Table 2). One patient (patient 6) received corticosteroids with no dasatinib interruption. Empiric antibiotics were administered to two patients.

Dasatinib-associated lung abnormalities resolved in seven patients and partially resolved in two patients. Respiratory symptoms and extrathoracic manifestations resolved within 1 week of dasatinib interruption. Pleural effusions regressed

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Time from CML Diagnosis to Dasatinib Treatment (mo)</th>
<th>Imatinib Status before Dasatinib Treatment</th>
<th>Time from Dasatinib Initiation to Lung Abnormality (d)</th>
<th>Cumulative Dasatinib Dose at Time of Lung Abnormality (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57</td>
<td>F</td>
<td>78</td>
<td>Primary resistance</td>
<td>256</td>
<td>35,840</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>F</td>
<td>37</td>
<td>Intolerance (constrictive bronchiolitis)</td>
<td>29</td>
<td>4,060</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>M</td>
<td>16</td>
<td>Intolerance (periipheral edema and upper airway angioedema)</td>
<td>463</td>
<td>49,660</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>M</td>
<td>10</td>
<td>Intolerance (hypersensitivity pneumonitis)</td>
<td>87</td>
<td>12,180</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>M</td>
<td>64</td>
<td>Secondary resistance</td>
<td>347</td>
<td>48,580</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>F</td>
<td>123</td>
<td>Secondary resistance</td>
<td>216</td>
<td>33,280</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>F</td>
<td>75</td>
<td>Secondary resistance</td>
<td>500</td>
<td>47,300</td>
</tr>
<tr>
<td>8</td>
<td>68</td>
<td>M</td>
<td>133</td>
<td>Secondary resistance</td>
<td>33</td>
<td>4,620</td>
</tr>
<tr>
<td>9</td>
<td>63</td>
<td>M</td>
<td>85</td>
<td>Secondary resistance</td>
<td>352</td>
<td>44,240</td>
</tr>
</tbody>
</table>

Definition of abbreviations: CML = chronic myeloid leukemia; F = female; M = male.

When lung manifestations were detected, all patients were receiving dasatinib 70 mg twice daily for CML in chronic phase after imatinib resistance or intolerance.

**Figure 1.** Different lung high-resolution computed tomography patterns observed in patients with dasatinib-related lung abnormalities. (A) Right-sided pleural effusion (patient 1); (B) ground-glass opacities in the upper left lobe (patient 2); (C) septal thickening in the right lower lobe (patient 3); (D) alveolar consolidation in the left lower lobe associated with pleural effusion (patient 4).
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Clinical Symptoms</th>
<th>Lung Abnormalities on HRCT</th>
<th>Pleural Fluid Analysis</th>
<th>BAL Fluid Analysis</th>
<th>Other Findings</th>
<th>Interventions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dyspnea, cough</td>
<td>Right-sided pleural effusion, bibasilar GGO</td>
<td>Lymphocytic exudate (87% Ly)</td>
<td>ND</td>
<td>No abnormalities detected in additional pulmonary investigations*</td>
<td>Dasatinib interruption, dasatinib reintroduction at a lower dose†</td>
<td>Resolution after drug interruption; no relapse after reintroduction</td>
</tr>
<tr>
<td>2</td>
<td>Dyspnea, cough, bronchospasm, arthralgia, myalgia, paresthesia</td>
<td>Diffuse GGO</td>
<td>ND</td>
<td>800 cells/μl 32% AM 67% Ly (CD4/CD8 ratio 4.8)</td>
<td>Neutrophilic exudate (80% Neu)</td>
<td>Antinuclear/ anti-DNA antibodies detected (1/1,600 level)</td>
<td>Dasatinib interruption</td>
</tr>
<tr>
<td>3</td>
<td>Chest pain</td>
<td>Bibasilar ST</td>
<td>ND</td>
<td>700 cells/μl 70% AM 30% Ly (CD4/CD8 ratio 2.9)</td>
<td>Lymphocytic exudate (62% Ly)</td>
<td>No abnormality observed in transbronchial biopsies; no abnormalities detected in additional pulmonary* or cardiac investigations</td>
<td>Diuretics (furosemide),* dasatinib interruption, dasatinib reintroduction at a lower dose†</td>
</tr>
<tr>
<td>4</td>
<td>Dyspnea, fever</td>
<td>Right-sided pleural effusion, bibasilar septal thickening, left alveolar condensation</td>
<td>Lymphocytic exudate (96% Ly)</td>
<td>400 cells/μl 69% AM 25% Ly 6% Neu</td>
<td>Lymphocytic infiltration observed in surgical pleural biopsy; Transient cytomegalovirus reactivation detected in blood (peripheral lymphocyte count 4,480/mm³)</td>
<td>Antibiotics (ceftriaxone and ofloxacin), dasatinib interruption</td>
<td>Resolution after drug interruption</td>
</tr>
<tr>
<td>5</td>
<td>Dyspnea</td>
<td>Right-sided pleural effusion, transient chylothorax (normalized at subsequent pleural fluid analysis)</td>
<td>Lymphocytic exudate (59% Ly)</td>
<td>ND</td>
<td>Marked myeloid infiltration observed in surgical pleural biopsy</td>
<td>Diuretics (furosemide),* dasatinib interruption</td>
<td>Partial resolution after drug interruption</td>
</tr>
<tr>
<td>6</td>
<td>Dyspnea, cough, fever</td>
<td>Mosaic pattern</td>
<td>ND</td>
<td>ND</td>
<td>No abnormalities detected in additional pulmonary* or cardiac investigations</td>
<td>Corticosteroids (prednisone)†</td>
<td>Resolution with corticosteroids</td>
</tr>
<tr>
<td>7</td>
<td>Cough</td>
<td>Right-sided pleural effusion, bibasilar GGO, and septal thickening</td>
<td>Lymphocytic exudate (48% Ly)</td>
<td>188 cells/μl 8% AM 92% Ly (CD4/CD8 ratio 3:3)</td>
<td>Lymphocytic infiltration observed in surgical pleural biopsy</td>
<td>Dasatinib interruption</td>
<td>Resolution after drug interruption</td>
</tr>
<tr>
<td>8</td>
<td>Dyspnea, cough, myalgia, chest pain</td>
<td>Bilateral pleural effusion, left lower lobe GGO</td>
<td>Neutrophilic exudate (39% Neu)</td>
<td>150 cells/μl 54% AM 9% Ly 36% Neu 1% Eo</td>
<td>Transient Epstein-Barr virus reactivation in blood detected (peripheral lymphocyte count 900/mm³)</td>
<td>Antibiotics (amoxicillin/ clavulanic acid and spiramycin), dasatinib interruption, dasatinib reintroduction at a lower dose†</td>
<td>Resolution after drug interruption; no relapse after reintroduction</td>
</tr>
<tr>
<td>9</td>
<td>Dyspnea</td>
<td>Bilateral pleural effusion</td>
<td>Lymphocytic exudate (85% Ly)</td>
<td>ND</td>
<td>No abnormality observed in blind pleural biopsy</td>
<td>Diuretics (furosemide),* dasatinib interruption, dasatinib reintroduction at a lower dose†</td>
<td>Resolution after drug interruption; relapse after reintroduction</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** AM = alveolar macrophages; BAL = bronchoalveolar lavage; Eo = eosinophils; GGO = ground-glass opacities; HRCT = high-resolution computed tomography; Ly = lymphocytes; Neu = neutrophils; ND = not done; ST = septal thickening.

* Pulmonary CT angiography, ventilation-perfusion lung scans, and venous ultrasonography.
† 40 mg twice daily.
‡ Echocardiography, scintigraphy, cardiac CT, and measurement of blood N-terminal pro–brain natriuretic peptide.
§ 40 mg/day for 3 days.
∥ 1 mg/kg/day initially, then tapered over 2 months.
within 1 month after treatment interruption (completely in four cases and partially in one case). In the seven patients with other lung abnormalities, HRCT returned to normal within 3 months of dasatinib interruption (five patients) or corticosteroid treatment (one patient), with one patient showing parenchymal septal thickening at last follow-up.

Dasatinib was reintroduced at a lower dose (40 mg twice daily) in four patients. Two patients (patients 1 and 8) had no recurrence of lung manifestations after an additional 2 or 4 months of follow-up (Table 2). Patient 3 remained free of respiratory symptoms throughout 6 months of low-dose treatment, although bibasilar septal thickening was detected at last the follow-up examination. Patient 9 experienced a relapse of bilateral exudative pleural effusion 5 months after dasatinib was reintroduced, which resolved with further treatment interruption.

DISCUSSION

In the present series of patients with dasatinib-related lung abnormalities, we found the following: (1) lung manifestations were frequent in the course of dasatinib treatment; (2) lung manifestations consisted not only of pleural effusions but also of lung parenchyma involvement; (3) pleural effusions were exudates and were not related to fluid retention, unlike those previously described with imatinib; (4) pleural and BAL fluid analysis showed mostly lymphocytic accumulation; and (5) lung manifestations resolved with dasatinib interruption and dasatinib could be reintroduced at a lower dose without recurrence of lung adverse events in most cases.

In our study, 6 of 40 patients (15%) treated with dasatinib for chronic-phase CML developed pleural effusions. This frequency is similar to pleural effusions reported as an unexplored adverse effect in patients with chronic-phase CML treated with dasatinib 70 mg twice daily in clinical trials after imatinib failure (4, 5). Interestingly, all six patients reported here had received dasatinib at the highest fractionated dose (70 mg twice daily). No patient developed peripheral edema, which occurs in most patients receiving imatinib (10). All pleural fluids analyzed were exudates, consistent with diuretic ineffectiveness in three patients. This finding, together with the high lymphocyte frequency both in pleural fluids and the pleural tissue of one patient, plus the absence of infection, suggests hypersensitivity or other immune-mediated reaction to the drug, as opposed to fluid retention.

Patient 5 had a nonblastic myeloid cell infiltration detected on surgical pleural biopsy. Pleural infiltration in CML is extremely rare. Unlike occasional cases in which pleural effusions have been described in blast-crisis CML (11–13), blast cells were not present in the pleural fluid. Extramedullary leukemia cell collections have been reported with imatinib (14), and it should be questioned if a similar phenomenon occurred in the dasatinib-treated patient described here.

In our study, seven patients developed lung parenchyma involvement (four with concurrent pleural effusions), which has not previously been reported in clinical trials. Although this might indicate left-sided heart dysfunction for some patients, normal left ventricular function observed on both echocardiography and scintigraphy and low levels of blood NT pro-BNP argue against this hypothesis (15). The presence of lymphocytic alveolitis on BAL fluid analysis (four patients), plus resolution by corticosteroids (one patient), the presence of autoantibodies (antinuclear/DNA; one patient), and extrathoracic manifestations (four patients) are consistent with an immune-mediated etiology. Interestingly, the only reported case of dasatinib-related pneumonia resolved with corticosteroids (16).

Patient 2 presented with autoantibodies and symptoms that might be associated with autoimmune disease, which disappeared after dasatinib interruption. Because dasatinib inhibits SRC-family kinases LCK and LYN, which are expressed in B and T lymphocytes and may be involved in the pathogenesis of autoimmune diseases such as systemic lupus erythematosus (17, 18), the potential for autoimmune effects should be considered. No autoimmune effects of dasatinib were reported in clinical trials. Inhibitory effects of dasatinib on immunologic SRC-family kinases or other signaling molecules (e.g., PDGFR-β) may contribute to lung complications.

In our case series, two of three imatinib-intolerant patients with dasatinib-related lung manifestations had previously experienced imatinib-related lung complications with a probable immune-mediated mechanism (constrictive bronchiolitis and hypersensitivity pneumonitis) (19). It is possible that some patients may be predisposed to lung manifestations with tyrosine kinase inhibitors, or alternatively, imatinib-induced lung abnormalities may increase the likelihood of similar events with dasatinib.

Dasatinib-related lung involvement may be dose related. In our study, dasatinib was reintroduced at 40 mg twice daily, and lung symptoms did not recur in three of four patients. This suggests that dasatinib-associated lung manifestations might be controlled with lower dosing. This hypothesis is supported by results from a phase III trial, which found that in patients with chronic-phase CML and imatinib resistance or intolerance, a lower proportion of patients experienced pleural effusions with a starting dose of dasatinib 100 mg administered once daily compared with the approved 70-mg twice-daily schedule (7 vs. 16%, respectively) (20). Of note, CML treatment responses in our study were maintained during treatment interruption.

Overall, lung physicians should be aware of the possibility of drug-related lung manifestations in patients receiving dasatinib. Our recommendations would be to stop dasatinib treatment and reintroduce the treatment with caution at a lower dose after lung manifestations have resolved. Corticosteroids may assist in management, although diuretics are likely to be ineffective because an immune-mediated mechanism is suspected. Whether similar events occur with other tyrosine kinase inhibitors in development, such as nilotinib, is under investigation.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

References


20. Shah NP, Kim DW, Kantarjian HM, Rousselot P, Dorfman-Llacer PE, Milone JH, Bleikardt E, Francis S, Hochhaus A. Dasatinib 50 mg or 70 mg BID compared to 100 mg or 140 mg QD in patients with CML in chronic phase (CP) who are resistant or intolerant to imatinib: one-year results of CA180034 [abstract]. J Clin Oncol 2007;25:A7004.