haematologica
the hematology journal

Early Release Paper

Extensive pleural and pericardial effusion in CML during treatment with dasatinib at 100 mg or 50 mg daily

by Maria-Theresa Krauth, Susanne Herndlhofer, Maria-Theresa Schmook, Gerlinde Mitterbauer, Ernst Schloegl, and Peter Valent

Haematologica 2010 [Epub ahead of print]

Citation: Krauth MT, Herndlhofer S, Schmook MT, Mitterbauer G, Schloegl E, and Valent P. Extensive pleural and pericardial effusion in CML during treatment with dasatinib at 100 mg or 50 mg daily. Haematologica. 2010; 95:xxx doi:10.3324/haematol.2010.030494

Haematologica (pISSN: 0390-6078, eISSN: 1592-8721, NLM ID: 0417435, www.haematologica.org) publishes peer-reviewed papers across all areas of experimental and clinical hematology. The journal is owned by the Ferrata Storti Foundation, a non-profit organization, and serves the scientific community with strict adherence to the principles of open access publishing (www.doaj.org). In addition, the journal makes every paper published immediately available in PubMed Central (PMC), the US National Institutes of Health (NIH) free digital archive of biomedical and life sciences journal literature.

DOI: 10.3324/haematol.2010.030494

Extensive pleural and pericardial effusion in CML during treatment with dasatinib at 100 mg or 50 mg daily

Running Title: Effusion-formation during low dose dasatinib

Maria-Theresa Krauth,[1] Susanne Herndlhofer,[1] Maria-Theresa Schmook,[2] Gerlinde Mitterbauer-Hohendanner[3], Ernst Schlögl,[4] and Peter Valent[1,5]

[1]Department of Medicine I, Division of Hematology & Hemostaseology, [2]Department of Radiology, and [3]Department of Laboratory Medicine; Medical University of Vienna, Austria; [4]Third Medical Department, Hanusch Hospital, Vienna, Austria, and [5]Ludwig Boltzmann Cluster Oncology, Vienna, Austria

Key Words: CML, BCR/ABL, Dasatinib, Side Effects

Funding
Fonds zur Förderung der Wissenschaftlichen Forschung in Österreich.

Correspondence
Peter Valent, M.D., Department of Internal Medicine I, Division of Hematology and Hemostaseology, Medical University of Vienna & Ludwig Boltzmann Cluster Oncology, Währinger Gürtel 18-20 A-1090 Vienna, Austria.
Phone: international +43.1 .404005488. Fax: international +43.1.404004030.
E-mail: peter.valent@meduniwien.ac.at

DOI: 10.3324/haematol.2010.030494

Abstract

Dasatinib is considered an effective drug in imatinib-resistant chronic myeloid leukemia. Although reported to be well-tolerated, severe events such as pleural or pericardial effusion, have been reported at 140 mg daily. We examined our chronic myeloid leukemia patients treated with dasatinib at 50 or 100 mg daily, and identified 4/13 patients who developed marked effusion-formation. In two patients, pleural and pericardial effusions grade III/IV were recorded. All 4 patients had received previous anti- chronic myeloid leukemia therapy, but none had pre-existing cardiac or pulmonary diseases. In 3 patients, dasatinib had to be discontinued despite treatment with diuretics and glucocorticosteroids. In conclusion, dasatinib-treated patients are at risk for the development of pleural and pericardial effusions even when the drug is administered at 100 mg or 50 mg daily. Therefore, all patients should be examined for pre-existing comorbidity and risk factors before starting dasatinib, and all should have repeated chest X rays during long-term dasatinib therapy.

DOI: 10.3324/haematol.2010.030494

Introduction

Therapy of imatinib-resistant chronic myeloid leukemia (CML) is an emerging challenge in clinical hematology.[1-3] In these patients, novel BCR/ABL tyrosine kinase inhibitors (TKI) are prescribed.[1-5] One highly effective second-generation BCR/ABL TKI is dasatinib.[5-8] This drug reportedly produces complete cytogenetic responses (CCyR) in a substantial number of imatinib-resistant patients.[6-10] Initially, dasatinib was announced as a dual inhibitor of Src kinases and BCR/ABL.[5] However, recent data suggest that dasatinib interacts with multiple kinase-targets[11] which may explain superior growth-inhibitory effects on CML cells, and also side effects. The initially approved standard dose of dasatinib was 70 mg per os twice daily. However, several studies have shown that dasatinib at 140 mg daily produces various side effects, including cytopenia and pleural effusions.[6-10,12,13] Therefore, the recommended standard dose of dasatinib has been reduced to 100 mg once daily in chronic phase CML. At this dose, dasatinib reportedly retains its anti-leukemic efficacy, but seems to be less toxic.[14] In patients in whom side effects occur with 100 mg dasatinib daily, dose reduction to 50 mg daily, treatment interruption, or switch to alternative drugs may be considered. However, long term data with low dose dasatinib are not available yet. Furthermore, some stimulating effects of dasatinib on immune cells such as enhancement of IgE-dependent histamine-liberation from basophils *in vitro*, are particularily seen at low concentrations (doses) of dasatinib.[15]

DOI: 10.3324/haematol.2010.030494

We report on 4 patients with imatinib-resistant CML who were treated with dasatinib at 100 mg or 50 mg dasatinib per os daily, and developed extensive pericardial and/or pleural effusions.

DOI: 10.3324/haematol.2010.030494

Design and Methods

Evaluation of consecutive CML patients treated with low dose dasatinib

Thirteen patients with CML received dasatinib at 100 mg or 50 mg daily for at least 3 months (range: 3-38 months) in our center (observation-period: March 2005 to June 2010). The patients´ characteristics are shown in Table 1. Two patients (CP) received dasatinib frontline in a phase II study (*clinicaltrials.gov identifier: NCT00481247*). All patients gave written informed consent.

Case Reports

Patient #1: In December 2007, a 70 year old female patient presented with imatinib-resistant CML-AP. CML was known since 2001. Previous therapies included interferon-alpha (IFNα), hydroxyurea (HU), and imatinib. No relevant comorbidities were known, except pneumonia in 2001 and Herpes zoster in 2003. In December 2007, the white blood count (WBC) was 20,000/µL, hemoglobin 12.5 g/dL, and platelets were 832,000/µL. Sequencing-analysis revealed *BCR/ABL* G250E. Therapy with dasatinib (100 mg daily) was initiated in January 2008. One week later, the patient developed pulmonary edema grade I. Dose-reduction to 50 mg dasatinib daily was followed by regression of symptoms. During the following months the patient entered MMR (BCR/ABL<0.01%). In February 2009, the patient developed symptomatic pleural effusions, and received diuretics and glucocorticosteroids. In March 2009, the patient presented with pleural effusion grade III and pneumonia requiring hospitalization. In May 2009, the patient also

relapsed with herpes zoster. Dasatinib was discontinued. Treatment with nilotinib was initiated in June 2009.

Patient #2: In February 2009, a 52 year old female patient presented with imatinib-resistant CML-AP. CML was known since 1993. In December 1995, she underwent allogeneic stem cell transplantation, SCT (HLA-identical unrelated donor). After SCT, she developed graft-versus-host disease (skin/liver). In November 1998, a cytogenetic relapse was diagnosed. Discontinuation of immunosuppressive therapy and donor-lymphocytes produced a transient response. In 2001, imatinib (400 mg daily) was started and resulted in CCyR and MMR. Previous comorbidities unrelated to SCT were a malignant melanoma (right leg) resected in 2000 and a carcinoma of the tongue resected in 2007. No pre-existing pulmonary or cardiac disorders were known. In February 2009, the WBC was 4,700/μL, hemoglobin 8.0 g/dL, and platelets were 962,000/μL. Cytogenetic analysis revealed a complex Ph+ karyotype. No *BCR/ABL* mutation was detected. In March 2009, dasatinib (100 mg/day) was started. A few days later, pneumonia and massive pleural effusions with consecutive right heart failure developed. The patient was hospitalized and received antibiotics and diuretics. Dasatinib was discontinued for 2 weeks. Thereafter, we tried once again to start dasatinib. However, in May 2009, she developed gastrointestinal bleeding, pleural effusions, and pneumonia. A few weeks later, massive pericardial effusion requiring intubation and transfer to the intensive care unit (pleural drainage and pericardial fenestration) occurred. Dasatinib was stopped and low dose prednisolone was initiated. During the following weeks, the clinical situation improved. In June 2009, nilolinib was started.

DOI: 10.3324/haematol.2010.030494

Patient #3: A 57 year old female patient without known comorbidities was diagnosed with CML-AP in June 2003. Imatinib (400 mg/day) was started. In February 2008, imatinib was discontinued because of intolerance and resistance (BCR/ABL V379I). Between April 2008 and September 2008, the patient received nilotinib. Despite prolonged pancytopenia, no major response was recorded, and in September 2008, *BCR/ABL* G250E and V379I were detected. In August 2009 dasatinib (100 mg/day) was started. However, after 4 months, dasatinib had to be discontinued because of grade IV cytopenia and pericardial effusion. Dasatinib was again started in January 2010 at 50 mg daily. However, after 1 month the patient developed a gastrointestinal infection as well as pericardial and pleural effusions. At that time, *BCR/ABL* T315I was detected and progression to BP recorded. She then received one cycle of polychemotherapy with cytarabine and mitoxantrone. After chemotherapy, the mutation status revealed a persistent *BCR/ABL* V379I, but no T315I or G250E. Since May 2010 the patient receives nilotinib (800 mg/day).

Patient #4: A 40 year old patient was diagnosed to have CP CML in April 2008. The blood count at diagnosis was: WBC 13,010/µl, hemoglobin 13.9 g/dL, and platelets 601,000/µL. The patient suffered from psoriasis vulgaris since 1987, and received continuous methotrexate p.o. No other relevant comorbidity was known. In April 2008, dasatinib at 100 mg daily was started. During the following months, the patients entered a CCyR and a MMR (BCR/ABL: 0.01% in May 2010). No relevant side effects were recorded until May 2010. Then, the patient developed bronchitis followed by severe dyspnoea. A chest X ray revealed marked pleural effusion

DOI: 10.3324/haematol.2010.030494

without pneumonia. The patient received diuretics and prednisolone (25 mg/day) which resulted in rapid improvement. Currently, the patient is still on dasatinib.

DOI: 10.3324/haematol.2010.030494

Results and Discussion

The most frequent relevant non-hematologic adverse event in dasatinib-treated patients is the occurrence of pleural effusions.[6-10,12,13] This side effect has also been referred to as serosal inflammation and apparently develops more commonly in patients with advanced disease.[16,17] In initial reports, the incidence of grade III or IV pleural effusions was reported to be rather low. On the other hand, effusion formation accumulates over time. More recently, it has been reported, that the risk of effusion formation is lower in patients treated with 100 mg dasatinib once daily compared to patients treated with 140 mg dasatinib.[14,17] However, even in freshly diagnosed patients treated with dasatinib at 100 mg daily, pleural effusions may develop.[17] The frequency of (symptomatic) pleural effusions in these patients was reported to be 13%, but only 1 out of 62 patients (2%) developed grade III/IV pleural effusion.[17]

We examined 13 CML patients treated with dasatinib at 50 or 100 mg daily in our center. Four of the 13 patients developed clinically relevant pleural or pericardial effusions: two of these 4 patients had grade III or IV effusions, and one developed a life-threatening pericardial effusion. In one of the two patients with CML CP who started frontline therapy with dasatinib at 100 mg daily, we also observed effusion formation. However, in this patient, only grade II pleural effusions developed which is in line with the data of Cortes et al.[17] The more aggressive clinical course in the other patients may be explained by the advanced disease-phase, previous therapy, and/or comorbidity.

DOI: 10.3324/haematol.2010.030494

Of the 13 patients examined, 4 had previously received 140 mg dasatinib daily. In these 4 patients, the dose of dasatinib was reduced to 100 mg or 50 mg daily because of pleural effusions. In the other 9 patients, the initial dose of dasatinib was 100 mg/day. Of these 9 patients, 2 CP patients received frontline dasatinib. One of these 2 patients developed pleural effusions. Three other patients also developed pleural effusions during treatment with dasatinib at 100 or 50 mg daily, and in two of them, pericardial effusions were also recorded. Of all 13 patients analyzed, 9 (69%) developed pleural effusions; and of the 9 patients who started with dasatinib at 100 mg/day, 5 (56%) developed pleural effusions.

In three of the 4 patients with marked effusion formation, dasatinib had to be discontinued. At that time, patient #1 was in CCyR and MMR, whereas patients #2 and #3 were in hematologic and molecular relapse (BCR/ABL 39.1% in patient #2 and 54.3% in #3). No *BCR/ABL* mutation was detected in patient #2. The BCR/ABL mutants detectable in patient #1 (G250E) and patient #3 (V379I) are known to be responsive to nilotinib. Therefore, we switched to nilotinib in these patients. During nilotinib therapy, patient #1 and patient #2 entered MMR with a decrease of BCR/ABL to 0.0% in patient #1 and to 0.008% in patient #2. In patient #3, no molecular follow up is available. Patient #4 is still in MMR and CCyR. So far, no further pleural effusions were recorded in the 4 patients.

The mechanisms underlying the development of effusion formation during dasatinib treatment are currently unknown. Most likely, several different factors contribute to effusion formation.[16,18] An interesting aspect is that dasatinib binds to and blocks major kinases of the immune system including Lyn, Btk, and Src, with consecutive deactivation of immune cells.[11,13,15] At low concentration, however, dasatinib may

even trigger the activation of certain immune cells. Likewise, low dose dasatinib even promotes IgE-dependent histamine release in basophils.[15] Although it has not formally been proven that basophil/mast cell activation and histamine release is involved in serosal inflammation/effusion formation caused by low dose dasatinib, it seems clear that dose-reduction of dasatinib may lower the risk of various side effects, but does not eliminate the risk of effusion-formation. This may hold also true for patients with freshly diagnosed CML.

One important factor concerning the risk of effusion formation may be pre-existing comorbidities, such as a cardiac or pulmonary disorders.[13,16] In addition, viral reactivation or infection, and an increase in activated lymphocytes (LGL cells) have been discussed as potential factors contributing to effusion formation.[19,20] In the four patients with pleural effusions (on 100 mg dasatinib) described in this study, no relevant pre-existing pulmonary or cardiac diseases were known. However, one patient was heavily pretreated and suffered from chronic GvHD of the skin. Therefore, we believe that several factors and comorbidities may act together to predispose for effusion-formation in patients treated with dasatinib.

In general, pleural effusions occurring during dasatinib are managed by treatment interruption or dose reduction as well as supportive therapy.[14,21,22] Whereas diuretics alone are usually without a long-lasting effect, glucocorticosteroids are often effective in these patients.[14,21,22] Therefore, we also applied low dose glucocorticoisteroids. However, because of the severity and recurrence of adverse events, dasatinib had to be discontinued in three of four patients.

An important aspect is early recognition and prevention of effusion-formation in CML patients treated with dasatinib. As mentioned above, one critical point is to screen for

possible comorbidities before starting dasatinib. A second important point is to recommend that dasatinib-treated CML patients have a repeated chest X-ray (e.g. once or twice a year) in their follow up even if no risk factors and no symptoms are recorded.

Currently, two BCR/ABL inhibitors, dasatinib and nilotinib, are available for treatment of imatinib-resistant CML, and both have shown similar efficacy in these patients.[5-9,23] It has also been described that both novel TKI can be administered in sequence when drug resistance or intolerance occurs.[24] Similarily, in our patients, we switched to nilotinib and so far, no relapse and no further effusion-events were recorded.

In summary, we describe 4 patients who received dasatinib at low dose and developed marked or even grade III/IV pericardial and/or pleural effusions. We recommend that all patients should be screened for relevant co-morbidities and potential risk factors before starting dasatinib (any dose) and all patients who receive long term dastatinib have repeated X-rays and careful monitoring of symptoms in their follow up.

Authorship and Disclosures

MTK. was the priciple investigator and takes the primary responsibility for the paper, MTK and PV wrote the paper, SH contributed administrative and logistic work, MTS performed radiologic studies, GM-H performed molecular studies, ES and PV recruited patients, and all co-authors approved the final version of the manuscript. PV received research grants from Novartis and from Bristol-Myers Suibb. Otherwise, the authors report no conflict of interest.

DOI: 10.3324/haematol.2010.030494

References

1. Martinelli G, Soverini S, Rosti G, Cilloni D, Baccarani M. New tyrosine kinase inhibitors in chronic myeloid leukemia. Haematologica. 2005;90(4):534-41.

2. Valent P. Emerging stem cell concepts for imatinib-resistant CML: implications for the biology, management, and therapy of the disease. Br J Haematol. 2008;142(3):361-78.

3. Saglio G, Ulisciani S, Bosa M, Cilloni D, Rege-Cambrin G. New therapeutic approaches and prognostic factors in chronic myeloid leukemia. Leuk Lymphoma. 2008;49(4):625-8.

4. Cortes J, Kantarjian H. Beyond dose escalation: clinical options for relapse or resistance in chronic myelogenous leukemia. J Natl Compr Canc Netw. 2008;6(S2):S22-S30.

5. Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science. 2004;305(5682):399-401.

6. Hochhaus A. Dasatinib for the treatment of Philadelphia chromosome-positive chronic myelogenous leukaemia after imatinib failure. Expert Opin Pharmacother. 2007;8(18):3257-64.

7. 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(24):2531-41.

8. Quintas-Cardama A, Kantarjian H, Jones D, Nicaise C, O'Brien S, Giles F, et al. Dasatinib (BMS-354825) is active in Philadelphia chromosome-positive chronic myelogenous leukemia after imatinib and nilotinib (AMN107) therapy failure. Blood. 2007;109(2):497-9.

9. 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(10):4143-50.

10. 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(8):3207-13.

11. Rix U, Hantschel O, Dürnberger G, Remsing Rix LL, Planyavsky M, Fernbach NV, et al. Chemical proteomic profiling of the BCR-ABL inhibitors imatinib, nilotinib, and dasatinib reveal different interaction networks and novel kinase and non-kinase targets. Blood. 2007;110(1):4055-63.

12. 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(25):3908-14.

13. Sillaber C, Herrmann H, Bennett K, Rix U, Baumgartner C, Böhm A, Herndlhofer S, Tschachler E, Superti-Furga G, Jäger U, Valent P. Immunosuppression and atypical infections in CML patients treated with dasatinib at 140 mg daily. Eur J Clin Invest. 2009;39(12):1098-109.

14. 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(19):3204-12.

15. Kneidinger M, Schmidt U, Rix U, Gleixner KV, Vales A, Baumgartner C, et al. The effects of dasatinib on IgE receptor-dependent activation and histamine release in human basophils. Blood. 2008;111(6):3097-107.

16. Kelly K, Swords R, Mahalingam D, Padmanabhan S, Giles FJ. Serosal inflammation (pleural and pericardial effusions) related to tyrosine kinase inhibitors. Target Oncol. 2009;4(2):99-105.

17. Cortes JE, Jones D, O'Brien S, Jabbour E, Ravandi F, Koller C, et al. Results of dasatinib therapy in patients with early chronic-phase chronic myeloid leukemia. J Clin Oncol. 2010;28(3):398-404.

18. 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(5):745-7.

19. Mustjoki S, Ekblom M, Arstila TP, Dybedal I, Epling-Burnette PK, Guilhot F, et al. Clonal expansion of T/NK-cells during tyrosine kinase inhibitor dasatinib therapy. Leukemia. 2009;23(8):1398-405.

20. Kreutzman A, Juvonen V, Kairisto V, Ekblom M, Stenke L, Seggewiss R, et al. Mono/oligoclonal T and NK cells are common in chronic myeloid leukemia patients at diagnosis and expand during dasatinib therapy. Blood. 2010;116(5):772-82.

DOI: 10.3324/haematol.2010.030494

21. Masiello D, Gorospe G 3rd, Yang AS. The occurrence and management of fluid retention associated with TKI therapy in CML, with a focus on dasatinib. J Hematol Oncol. 2009;2:46.

22. Mauro MJ, Deininger MW. Management of drug toxicities in chronic myeloid leukaemia. Best Pract Res Clin Haematol. 2009;22(3):409-29.

23. Rosti G, Castagnetti F, Gugliotta G, Palandri F, Martinelli G, Baccarani M. Dasatinib and nilotinib in imatinib-resistant Philadelphia-positive chronic myelogenous leukemia: a 'head-to-head comparison'. Leuk Lymphoma. 2010;51(4):583-91.

24. Mauro MJ. Appropriate sequencing of tyrosine kinase inhibitors in chronic myelogenous leukemia: when to change? A perspective in 2009. Curr Opin Hematol. 2009;16(2):135-9.

DOI: 10.3324/haematol.2010.030494

Table 1. Patients´ characteristics.

#No	gender f/m	age yrs	CML phase	karyotype	*BCR/ABL* mutations* before DASA	*BCR/ABL* mutations* during DASA	previous therapy	start dose DASA mg/day	pleural effusion (grade)
#01	f	71	CP	46,XX,t(9;22)	G250E/G	n.d.	IFN, HU, IM	100_50*+	(III)
#02	f	52	AP	t(9;22), complex	no	no	IFN, HU, alloSCT, IM	100	+ (IV)
#03	f	56	AP	t(9;22), complex	G250E V369I	G250E T315I	ARA-C, IM, Anagrelide, Nilotinib,	100	+ (II)
#04	m	40	CP	46,XY,t(9;22)	n.d	n.d.	no	100	+ (II)
#05	m	54	CP	t(9;22), complex	n.d.	n.d.	HU	100	-
#06	m	53	CP	46,XY,t(9;22)	F359I	no	IFN, HU, Nilotinib	100	-
#07	m	60	CP	46,XY,t(9;22)	n.d.	E255K	HU, IFN, alloSCT, IM, Nilotinib	100	-
#08	m	42	CP	46,XY,t(9;22)	L387M/L	L387M/L, G250E , E255K, and T315I	IM, HU	100	-
#09	f	43	CP	46,XX,t(9;22)	no	no	IM, HU, Ara-C, Nilotinib	100	+ (I)
#10	f	70	AP	46,XX,t(9;22)	M244V	no	HU, IM	140	+ (II)
#11	f	73	AP	46,XX,t(9;22)	A1094R, M244M/V	F317L	HU, Ara-C, IFN, IM, RAPA	140	+ (II)
#12	f	42	AP	47,XX,+8,t(9;22)	Y253Y/H	no	IFN, Ara-C, IM, autoSCT, Rapa, HU	140	+ (II)
#13	f	71	CP	46,XX,t(9;22)	G250E/G F317L/F	F317L	HU, IFN, IM	140	+ (II)

f: female; m: male; yrs: years; DASA: dasatinib; WBC: white blood count; Hb: hemoglobin; PLT: platelet count; AP: accelerated phase; CP: chronic phase; HU: hydroxyurea; IFN: interferon-alpha; IM: imatinib; Ara-C: cytosine arabinoside; autoSCT: autologous hematopoietic stem cell transplantation; alloSCT: allogeneic SCT; RAPA, rapamycin; *All parameters except *BCR/ABL* mutations were recorded shortly before start with dasatinib. *BCR/ABL* mutations were examined before dasatinib and during treatment with dasatinib as long as BCR/ABL was detectable. *In this patient, the dose of dasatinib was reduced from 100 mg to 50 mg dasatinib daily after the first week of treatment.

DOI: 10.3324/haematol.2010.030494

Figure 1. Radiographic findings during dasatinib therapy. **A.** X-ray of chest in patient #2 one day before starting dasatinib. No pleural effusions were noted. **B.** Six weeks after initiation of dasatinib, massive pleural effusions were recorded when the patient suffered from dyspnoea. **C.** After discontinuation of dasatinib, pleural effusions disappeard almost completely. The patient is currently treated with nilotinib.