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Case Report

A CML case with resistant pleural effusion with tyrosine kinase inhibitor treatment

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Abstract: Dasatinib-related pleural effusion has a relationship with the development of large granulocyte lymphocytosis and complete molecular response in CML patients. Here we present a CML case that was treated with various TKIs and suffered from massive life-threatening pleural effusion and large granular lymphocytosis observed in his blood film. 52 years old male patient who was diagnosed as CML in 2008, first time suffered from dyspnea in January 2014. Chest film revealed bilateral pleural effusion which was considered to be side-effect of dasatinib treatment. In his blood film, a few large granular lymphocytes were present. We have given nilotinib 2×400 mg instead of dasatinib. In August 2015, he had dyspnea and on chest film, again bilateral pleural effusion was observed. He was under full cytogenetic and molecular remission. Our patient has progressive intractable pleural effusion during hospitalization. Two pigtail catheters were placed. In January 2016 pleurodesis was performed. He is still under close control without any TKI treatment. The clonal expansion of large granular lymphocytes in patients who were given dasatinib has been shown to be related with pleural effusion and improved outcome. Nearly for 3 months without any TKI treatment, our patient remained under complete remission. This finding in our patient could be a sign of good prognosis since pleural effusion and large granular lymphocytosis related with improved outcome in CML patient. To conclude, in CML patients the pleural effusion could be resistant and life-threatening adverse effect of TKIs however the existence of large granular lymphocytosis may indicate better prognosis.

Keywords: Dasatinib, pleural effusion, CML

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disease which is related with the Philadelphia chromosome t (9;22) (q34;q11) that results in the BCR-ABL fusion gene. Tyrosine kinase inhibitors (TKIs) inhibit the initiation of the Bcr-Abl pathway [1-3]. TKIs are usually very well tolerated; most side effects are mild and majority cases can continue treatment. Pleural effusion and pulmonary infiltrates are common side effects of dasatinib which were documented in 14-60% of patients [4]. This adverse effect of dasatinib has a relationship with the development of large granulocyte lymphocytosis [5, 6]. It is very interesting that there is an association between a side effect like pleural effusion and complete molecular response in CML patients who were given dasatinib. Herein, we aimed to report a CML case that was treated with various TKIs and suffered from massive life-threatening pleural effusion and large granular lymphocytosis observed in his blood film.

Case report

52 years old male patient was under control of our clinic since year 2008 with the diagnosis of CML. In his anamnesis, he had known history of coronary artery disease since year 2005. Two coronary stents were implanted to his coronary veins. After this procedure, he was under control of the cardiology clinic and his electrocardiography and treadmill test was normal. His echocardiography investigation revealed 60-65% ejection fraction and normal left ventricular systolic functions. After the diagnosis of CML, he had been given imatinib mesylate 400 mg 1×1. Cytogenetic, molecular and hematologic remission was achieved in 2008. In November 2009 molecular, cytogenetic and hematologic response was lost, therefore he had been given second generation TKI, dasat-

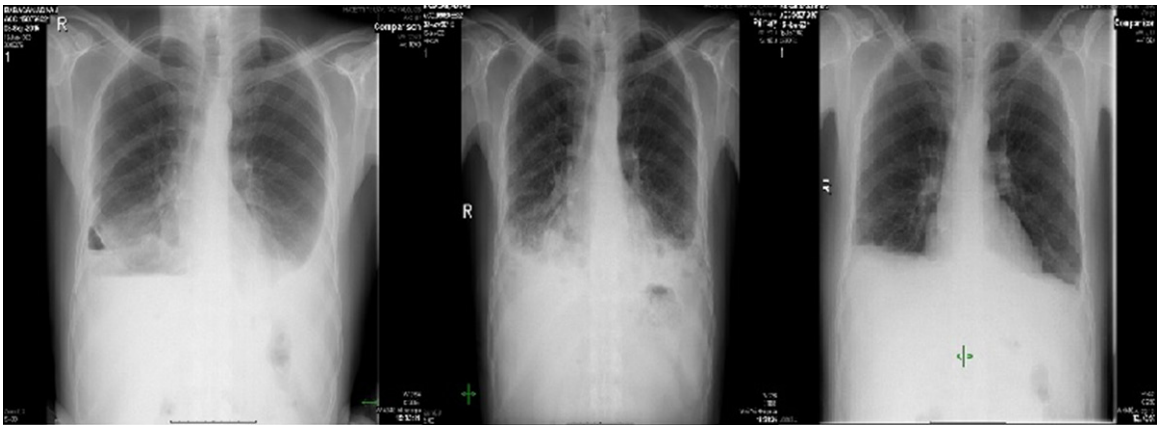

Figure 1. Progressive intractable pleural effusion in multi-TKI resistant CML patient. Chest films of the patient on admission to hospital (left), 1 month after the admission (middle) and 2 months after admission (right) were given in the figure.

inib 1×100 mg. 3 months later again hematologic, molecular and cytogenetic response was achieved. He has tolerated the drug very well and he had no adverse effects. In January 2014, our patient first time suffered from dyspnea. Chest film revealed bilateral pleural effusion which was considered to be side-effect of dasatinib treatment. The sample from his pleural effusion was exudative. His laboratory tests were resulted as, hemoglobin 8.3 gr/dl, white blood cell 12.4×10^3/µl, platelet 626×10^3/µl, ALT 21 U/l, AST 16 U/l, creatinine 1.05 gr/dl. In his blood film, a few large granular lymphocytes were present. With dose reduction and other supportive treatments with steroid treatment our patient's dyspnea and pleural effusion reduced. After this complication we have switched our TKI choice to nilotinib 2×400 mg. His hematologic, molecular and cytogenetic response persists during these years. In August 2015, he again had complaint about dyspnea during his follow-ups. On chest film, again bilateral pleural effusion was observed. In October 2015, he was hospitalized in order to investigate and treat his pleural effusion. He was under full cytogenetic and molecular remission. Our patient has progressive intractable pleural effusion during hospitalization (**Figure 1**). The other reasons of pleural effusion were excluded including the mycobacterium tuberculosis infection. Two pigtail catheters were placed in order to drain the pleural effusion that had caused dyspnea. A total of 300 cc/day hemorrhagic liquid come out of the drain. The type of pleural effusion was exudative. Because of pleural effusion under nilotinib, TKI treatment was switched to bosutinib. Bosutinib 1×500 mg was given to our patient however with nearly 3 weeks of this treatment there was no difference in the size of pleural effusion. Therefore, all TKI treatment was stopped and patient was taken under close control with laboratory test in case of a hematologic relapse. He was discharged from the hospital under the condition of draining the pleural liquid until the liquid mass fall under 100 cc/day. In January 2016, the mass of right pleural fell to 20 cc/day and pleurodesis was performed to right pleura. He is still under close control of our clinic without any TKI treatment.

Discussion

Pleural effusion and/or pulmonary infiltrates are common complications of dasatinib [7]. 35% of cases treated with dasatinib encountered pleural effusions, mostly exudative, some of which have required thoracentesis, insertion of a chest tube, pleurodesis, and/or interruption or reduction of drug dosage. In a trial it was showed that with the dose of 100 mg/day dasatinib the incidence of pleural effusion was reduced without disturbing short or long term efficacy [8]. It is important to exclude the other reasons of pleural effusion in patients who were complicated with pleural effusion and using TKIs [9]. In our patient we have excluded the other reasons of pleural effusion. The relationship between pleural effusion and the development of clonal large granular lymphocytes is vital [10]. Data of dasatinib-associated large granular lymphocytosis obtained from ret-

Table 1. What to do in dasatinib-induced pleural effusion

	Properties
Pharmacobiology	*Pleural effusion is observe more in patients who have peripheral lymphocytosis. *In most cases the pleural effusions are exudative. There is lymphocyte dominance in effusions. Sometimes effusions may be transude or chylous. *The lymphocyte dominance and lymphocyte infiltration in pleural biopsy indicates the immunological response. Better prognosis in CML is related with lymphocytosis. *The pathogenesis is not yet clarified however there some hypotheses have been made: (1) blocking of PDGFR-P by dasatinib, (2) rise in permeability and/or pleural/pulmonary vasculature due to block of SRC family kinase, (3) hypersensitivity or immune-relatedresponse to dasatinib rather than fluid reaction.
Clinical picture	*The mean time to develop pleural effusion under dasatinib is 200 days. *Most of the pleural effusions with dasatinib are asymptomatic.
Treatment	*Dasatinib leads to less pleural effusion when given daily than twice daily without a change in treatment response. *The mean time to develop pleural effusion under dasatinib is more than 200 days who were given 100 mg dasatinib daily. *5% of the patients do not tolerate dasatinib because of pleural effusion. *If dasatinib related pleural effusion could not be taken under control, the other TKIs should be administered.
Outcome	*Dasatinib-induced pleural effusion indicates better prognosis however serious effusions contain risks. *Patients who were given dasatinib and imatinib should be followed-up closely. *Pulmonary artery hypertension may develop under dasatinib treatment.

rospective studies of CML and Ph + ALL. Its prevalence throughout dasatinib series differs between 27% and 64% [11]. The large granular lymphocytosis is also related with dasatinib dosage. It was shown that large granular lymphocytosis was detected in 7% compared to 16% of the cases which were given daily versus twice daily dasatinib, respectively [12]. In the literature it was stated that clonal expansion of large granular lymphocytes in patients who were given dasatinib therapy has been shown to be related with pleural effusion and improved outcome [13]. The mechanism underlying the detected effect in blood cells due to dasatinib is not clarified. The SRC family kinases have an important effect on leukocyte trafficking between intravascular regions and tissues that are significant in management of cell adhesion and movement [14]. The inhibition of SRC family kinases by dasatinib may be the reason of the alterations of leucocytes [15]. Treatment choices for controlling effusions greater than grade 2 are temporary dasatinib discontinuation until resolution. Decreasing the dosage and/or schedule change (once daily) are other significant actions to avoid fluid accumulation. Supportive care with diuretics and steroids could be used. Thoracentesis may be required in patient with large or recurrent or those unresponsive to treatments [16]. We have also performed dose reduction, supportive treatment and steroids; however our patients' pleural effusion persisted. We have switched the TKI treatment but we could not administer ponatinib because of the history of cardiac disease in our patient. At last thoracentesis was performed to our patient with the discontinuation of TKI treatment. Nearly for 3 months without any TKI treatment, our patient remained under complete remission. This finding in our patient could be a sign of good prognosis since pleural effusion and large granular lymphocytosis related with improved outcome in CML patient. In CML patient treatment should be personalized [17]. The management of TKI related pleural effusion is also very important in the treatment approach of CML cases (**Table 1**). To conclude, in CML patients the pleural effusion could be resistant and life-threatening adverse effect of TKIs however the existence of large granular lymphocytosis may indicate better prognosis.

Disclosure of conflict of interest

None.

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References

[1] Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science 2004; 305: 399.

[2] Verstovsek S, Golemovic M, Kantarjian H, Manshouri T, Estrov Z, Manley P, Sun T, Arlinghaus RB, Alland L, Dugan M, Cortes J, Giles F, Beran M. AMN107, a novel aminopyrimidine inhibitor of p190 Bcr-Abl activation and of in vitro proliferation of Philadelphia-

positive acute lymphoblastic leukemia cells. Cancer 2005; 104: 1230.
[3] Weisberg E, Manley PW, Breitenstein W, Brüggen J, Cowan-Jacob SW, Ray A, Huntly B, Fabbro D, Fendrich G, Hall-Meyers E, Kung AL,Mestan J, Daley GQ, Callahan L, Catley L, Cavazza C, Azam M, Neuberg D, Wright RD, Gilliland DG, Griffin JD. Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl. Cancer Cell 2005; 7: 129.
[4] Lavallade H, Punnialingam S, Milojkovic D, Bua M, Khorashad JS, Gabriel IH, Chaidos A, Olavarria E, Goldman JM, Apperley JF, Marin D. Pleural effusions in patients with chronic myeloid leukaemia treated with dasatinib may have an immune-mediated pathogenesis. Br J Haematol 2008; 141: 734-747.
[5] 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 leukaemia in chronic phase and efficacy is uneffected in patients who develop pleural effusion. Cancer 2010; 116: 377-386.
[6] Mustjoki S, Ekblom M, Arstila TP, Dybedal I, Epling-Burnette PK, Guilhot F, Hjorth-Hansen H, Höglund M, Kovanen P, Laurinolli T, Liesveld J, Paquette R, Pinilla-Ibarz J, Rauhala A, Shah N, Simonsson B, Sinisalo M, Steegmann JL, Stenke L, Porkka K. Clonal expansion of T/NKcells during tyrosine kinase inhibitor dasatinib therapy. Leukemia 2009; 23: 1398-1405.
[7] Bergeron A, Rea D, Levy V, Picard C, Meignin V, Tamburini J, Bruzzoni-Giovanelli H, Calvo F, Tazi A, Rousselot P. Lung abnormalities after dasatinib treatment for chronic myeloid leukaemia. Am J Respir Crit Care Med 2007; 176: 814-818.
[8] 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.
[9] 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.
[10] Apperley JF, Cortes JE, Kim DW, Roy L, Roboz GJ, Rosti G, Bullorsky EO, Abruzzese E, Hochhaus A, Heim D, de Souza CA, Larson RA, Lipton JH, Khoury HJ, Kim HJ, Sillaber C, Hughes TP, Erben P, Van Tornout J, Stone RM. Dasatinib in the treatment of chronic myeloid leukemia in accelerated phase after imatinib failure: the START a trial. J Clin Oncol 2009; 27: 3472-3479.
[11] Paydas S. Dasatinib, large granular lymphocytosis, and pleural effusion: useful or adverse effect? Crit Rev Oncol Hematol 2014; 89: 242-247.
[12] Deininger MW, O'Brien SG, Ford JM, Druker BJ. Practical management of patients with chronic myeloid leukemia receiving imatinib. J Clin Oncol 2003; 21: 1637-1647.
[13] Nagata Y, Ohashi K, Fukuda S, Kamata N, Akiyama H, Sakamaki H. Clinical features of dasatinib-induced large granular lymphocytosis and pleural effusion. Int J Hematol 2010; 91: 799-807.
[14] Zarbock A, Ley K. Protein tyrosine kinases in neutrophil activation and recruitment. Arch Biochem Biophys 2011; 510: 112-119.
[15] Imagawa J, Tanaka H, Matsumoto K, Morito K, Harada Y, Harada H. A sharp fluctuation in peripheral blood cells shortly after dasatinib administration. In J Hematol 2012; 96: 194-199.
[16] Bergeron A, Rea D, Levy V, Picard C, Meignin V, Tamburini J, Bruzzoni-Giovanelli H, Calvo F, Tazi A, Rousselot P. Lung abnormalities after dasatinib treatment for chronic myeloid leukemia. Am J Crit Care Med 2007; 176: 814-818.
[17] Haznedaroglu IC. Current concerns of undertreatment and overtreatment in chronic myeloid leukemia based on European LeukemiaNet 2013 recommendations. Expert Opin Pharmacother 2013; 14: 2005-2010.