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A Patient with Pleural Effusion Related to Dasatinib

Dasatinib İlişkili Plevral Efüzyonlu Bir Hasta

CASE REPORT
OLGU SUNUMU

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ABSTRACT
ÖZET

Dasatinib is a tyrosine kinase inhibitor which is used for the treatment of patients with chronic myeloid leukemia (CML) resistant or intolerant to imatinib. Dasatinib can cause fluid retention in some patients, leading to peripheral edema and pleural effusion. Recognition of these symptoms as a potential complication of dasatinib will help prevent unnecessary investigations and facilitate adequate management. We report a patient with blastic phase CML. In patients with advanced phase CML an initial dose of dasatinib is recommended as 70 mg twice daily. We observed that 100 mg once daily dose of dasatinib could control the blastic phase of CML with less toxicity.

Key words: Chronic, dasatinib, malignant, myeloid leukemia, pleural effusion

Dasatinib imatinib dirençli veya tolere edemeyen kronik miyeloid lösemili (KML) hastalarda kullanılan bir tirozin kinaz inhibitörüdür. Dasatinib peripheral ödem ve plevral efüzyona yol açan, sıvı retansiyonuna sebep olabilir. Bu potansiyel komplikasyonların bilinmesi gereksiz araştırmaları önleyecek ve tedaviyi kolaylaştıracaktır. Biz bu yazıda dasatinib tedavisi sonrası plevral efüzyon gelişen blastik faz KML'li bir hastayı rapor ettik. İleri faz KML olan hastalarda, günde iki kez 70 mg dasatinib başlangıç dozu önerilir. Biz 100 mg tek dozun daha az toksisite ile etkili olabildiğini gözlemledik.

Anahtar kelimeler: Dasatinib, kronik, malign, miyeloid lösemi, plevral efüzyon

Introduction

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disease characterized by the Philadelphia (Ph) chromosome, which arises from the reciprocal chromosomal translocation t (9;22) (1). This genetic aberration arises from an exchange of genetic material between chromosomes 9 and 22, which results in the fusion of the Breakpoint Cluster Region (BCR) and the Abelson Leukemia Virus (ABL) genes (2). This fusion gene encodes a chimeric protein, BCR-ABL (Breakpoint Cluster Region-Abelson) that is associated with uncontrolled activity of the ABL tyrosine kinase (3). Dysregulation of ABL tyrosine kinase activity, consequent to the BCR-ABL transcript, emerged as a critical event in the CML pathogenesis, and is capable of transforming hematopoietic cells (4).

In the late 1980s, among the compounds with inhibitory activity against protein kinases, imatinib mesylate emerged as a promising compound capable of inhibiting all the ABL tyrosine kinases, including BCR-ABL (5). Imatinib mesylate is now first-line therapy for newly diagnosed CML and potently inhibits BCR-ABL and blocks proliferation and growth of tumor cells expressing BCR-ABL (5-7). Despite the outstanding results achieved with imatinib, approximately 20% to 30% of patients may either not respond to therapy or eventually develop resistance or intolerance to the drug (8). Dasatinib offers a new treatment option for patients with CML or Ph-positive ALL who are either unable to tolerate or resistant to previous therapy, including imatinib. Dasatinib has been found to be more effective in eliciting a cytogenetic or hematologic response and is better tolerated than high-dose imatinib (9). Because of the greater potency of dasatinib against native BCR-ABL, dasatinib may have activity in patients with imatinib resistance caused by BCR-ABL over expression (10, 11).

Even though 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 (12). However, a detailed description of these adverse events has not been published. Here, we described the clinical management of a patient with pleural effusion related to dasatinib and the effectiveness of dasatinib 100 mg/day.

Case Report

A 72-year-old woman was diagnosed with CML, chronic phase, in July 2007. Cytogenetic tests revealed the presence of the Ph chromosome t (9;22). She was treated with 400 mg of imatinib once daily and a complete hematological and cytogenetic response was achieved. In February 2009, the patient experienced a hematologic relapse and deteriorated clinically. The peripheral blood smear revealed CML consistent with the accelerated

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phase. The dose of imatinib was switched to 600 mg once daily owing to the development of resistance to imatinib. After 3 months follow-up blastic transformation was detected. Because of the patient's age, and not suitable clinically, she was not given intensive systemic chemotherapy. She was then administered dasatinib 70 mg twice daily. A month after dasatinib was started the patient developed dyspnea, cough, and chest pain. A chest radiograph revealed moderate unilateral pleural effusion which could not be attributed to known causes and was therefore deemed to be treatment-related (Figure 1a). Transthoracic echocardiography (left ventricular ejection function % 65 and no pericardial effusion) and chest computed tomography and others laboratory tests were performed to determine the etiology of the pleural fluid. Finally, except for a left sided unilateral pleural effusion, no abnormalities which could be related with pleural effusion were detected.

Biochemical analysis of thoracentesis was identified as a transudate (according to the Light criteria) and cytological analysis revealed moderate lymphocyte and mesotel. Malignant cells or microbiological organisms were not demonstrated. On physical examination, no edema was present on any other parts of the body (orbital, pretibial etc.). Since the effusion was thought to be related with dasatinib, dasatinib treatment was temporarily suspended and a small dose of steroid (Methyl prednisolone, 40 mg/day) and diuretic (Furosemid, 20 mg/day) were administered for 10 days. Fifteen days after discontinuation of dasatinib, the patient's clinical symptoms and radiological images disappeared completely (Figure 1b). After recovery, dasatinib was restarted in a new dose schedule, 100 mg once daily. After restarting of new dose schedule of dasatinib, there was to date no recurrence of pleural effusion according to chest radiography or any symptom related with pleural effusion.

Discussion

Dasatinib is a potent inhibitor of BCR-ABL. Although long-term survival data is not present, several studies have confirmed the efficacy of dasatinib in the setting of imatinib failure (13, 14). In a phase-II study on the use of dasatinib in patients with imatinib -resistant/intolerant disease in the chronic phase, complete hematologic and major cytogenetic response was seen in 90% and 52% of patients, respectively (14).

The most commonly reported grade 3/4 adverse events associated with dasatinib are those connected with hematological, gastrointestinal and respiratory system (1, 13, 14). Pleural effusions were observed in 5% to 35% of dasatinib-treated patients, although the highest incidence was noted in patients in advanced phases of CML (15). Pleural effusion can develop at any stage of treatment with dasatinib. The median time taken to develop pleural effusion is reported as 5 weeks (range, 1 to 107 weeks), occurring within the first 12 months in 90% of patients on dasatinib therapy (16).

Even though the mechanism of fluid retention related with dasatinib treatment remains unclear, immune-mediated mechanisms have been suggested as a possible explanation for pleural effusion rather than fluid retention (12). Several risk factors have been identified for this complication. Previously, prior cardiac history, hypertension and a twice daily schedule were found to be risk factors (16, 17). Recently, this adverse association related with twice daily schedule is reinforced by a few different studies (2, 18). In addition to a safety profile of the once daily schedule of dasatinib, the rate of discontinuation due to toxicity was lower compared with twice daily, suggesting that the once daily schedule is better tolerated than a twice-daily schedule (18). Furthermore, the hematologic and cytogenetic response rates of the once-daily regimen were similar to those patients treated with twice-daily regimen (1). It should be emphasized that adjusting the dose schedule of dasatinib does not allow any deficiency in the activity of dasatinib in hematological or cytogenetic response.

Pleural effusion, consistent with the literature, developed a month after initial treatment of dasatinib in the presented case. After discontinuation of dasatinib, methyl prednisolone and diuretic were administered. Just two weeks after discontinuation of dasatinib, the patient's complaints resolved completely. Steroid responsiveness of

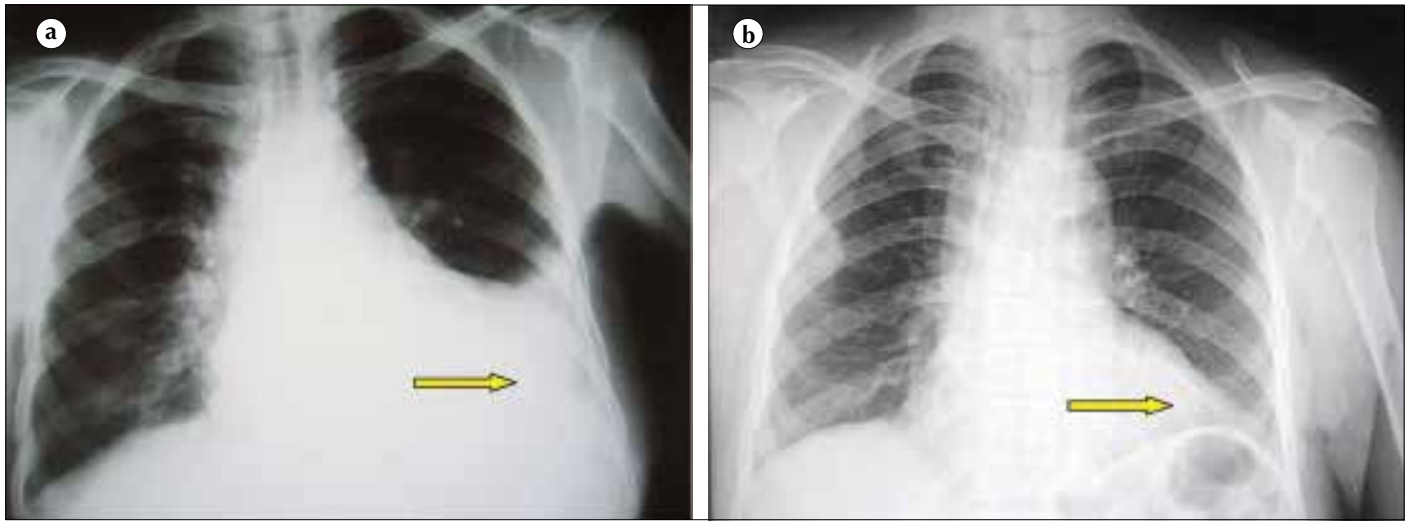

Figure 1. a) Seventy-two-year-old woman was diagnosed with blastic phase CML. Left pleural effusion (arrow) related to dasatinib (70 mg twice daily). b) Fifteen days after discontinuation of dasatinib, the patient's clinical symptoms and radiological images disappeared completely

our patient suggests that the immune mechanism is responsible for pleural fluid collection. After restarting treatment with an adjusted dose of dasatinib (from 70 mg twice daily to 100 mg once daily), in the six-month follow-up, pleural effusion had not developed and also complete hematological and minor cytogenetic responses were obtained. Although the recommended initial dose of dasatinib is 70 mg twice daily for patients with advanced phase CML, due to the poor prognosis (2), we observed that a 100 mg once daily dose of dasatinib could control the blastic phase of CML with less toxicity. In one of the recent studies, it has been proposed that the noncontinuous target inhibition with once-daily dosing may explain the lower toxicity of dasatinib, indicating that once-daily dosing resulted in transient BCR-ABL inhibition (18). Furthermore, it has been claimed that continuous BCR-ABL exposure may not be required for efficacy of dasatinib (18).

Conclusion

We believe that administration of dasatinib on initial treatment, a once daily schedule may be considered as a standard in all phases of CML.

Conflict of interest

No conflicts of interest were declared by the authors.

Authors' contributions: The manuscript was prepared by RE and NT under the supervision of CD. AŞ analyzed the data and wrote the manuscript. All authors read and approved the final manuscript.

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