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Original Article

Investigations of Risk Factors and Management of Pleural Effusion associated with Dasatinib Therapy for Chronic Myelogenous Leukemia after Imatinib Failure

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ABSTRACT:

Background:

Treatment of chronic myeloid leukemia (CML) has experienced dramatic changes in the most recent decade. Analyzing the atomic pathways that prompt the advancement of this infection brought about the improvement of focused treatment against the sub-atomic driver of CML, to be specific the aberrantly activated tyrosine kinase BCR-ABL1. Dasatinib has shown tough clinical reactions in patients, both as first-line and ensuing lines of treatment. We examined the hazard elements and administration of pleural emission related with dasatinib treatment for chronic myelogenous leukemia (CML) after failure of imatinib. **Materials and Methods:** 270 patients with imatinib resistant/ - intolerant CML in chronic stage (CML-CP) got dasatinib 100mg once every day, 50mg twice daily, 140mg once daily, or 70 mg twice daily. We analysed patients with CML treated with dasatinib for 3 years for the development of pleural effusion. **Result:** Pleural effusion happened in 32 patients, including 24% of those treated in chronic stage (CP), 46% in accelerated stage (AP), and 29% in blast stage (BP). By examination, history of heart illness, hypertension, and utilization of a twice-every day plan were recognized as variables related with occurrence of pleural effusions. Effusions were exudative in 67% of the assessable cases. In a few patients, effusions were related with reversible additions of right ventricular systolic pressure. **Conclusion:** Pleural emanations happen amid dasatinib treatment, especially among patients in AP or BP. A twice-day by day schedule may bring about a higher frequency of pleural effusion. Close checking and opportune mediation may enable patients to proceed with treatment and accomplish the coveted clinical advantage.

Keywords: Dasatinib, imatinib, TKI, chronic myeloid leukaemia, autoimmunity, toxicity, pleural effusions.

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INTRODUCTION:

Chronic myeloid leukemia (CML) emerges by clonal development of an atypical myeloid precursor cell in the bone marrow. It is normally characterized into three unmistakable clinical stages, in particular the chronic phase (CP), acceleration phase, and blast crisis, the last of which looks like acute leukemia and presentations an extremely poor prognosis.[1] The pathogenetic culprit in CML is the adjusted complementary translocation between chromosomes 9 and 22 producing the supposed Philadelphia chromosome, perceivable in roughly 95% of all CML patients.[2] On an atomic level, the translocation brings about the combination of the c-abl proto-oncogene from chromosome 9 with the breakpoint group (BCR)- quality from chromosome 22, yielding an abnormally actuated tyrosine-kinase named BCR-ABL1. This all over again oncoprotein drives the threatening change of the myeloid forerunner cell by phosphorylation of downstream effector pathways in charge of development and expanded survival of the antecedent cells.[3]

Dasatinib was endorsed for the second-line treatment of CML-CP after imatinib disappointment because of resistance. Dasatinib was initially created as a Src-kinase inhibitor, yet showed powerful movement as an ABL-inhibitor also. Besides, it likewise ties suppress different kinases, for example, c-Kit or platelet determined development factor β-receptor.[4] As expressed above, to apply its inhibitory function, imatinib requires the ABL tyrosine kinase to be in its closed and thus inactive conformation, though dasatinib hinders the kinase in its dynamic compliance. Endorsement of dasatinib was in this way reached out to all periods of CML and additionally Ph+ intense lymphoblastic leukemia (ALL) and resistance or intolerance to past treatment including imatinib, and as of

late, to recently analyzed CML-CP. In this audit, we compress the information on the viability and security of dasatinib as a second line treatment in CML-CP patients resistant or intolerant to treatment with imatinib.[5] The symptoms related with dasatinib treatment are prevalently gentle or direct and are self-constraining or resolve following strong care. Dasatinib is related with correspondingly positive rates of treatment consistence and lethality related withdrawal. Pleural effusion is generally an uncommon medication related unfavorable event, ordinarily bringing about the requirement for some sort of mediation. Normal side effects of pleural effusion incorporate cough, exhaustion, and dyspnea, which may influence the patient's nature of life.

Danger of effusions exists with all the tyrosine kinase inhibitors (TKIs) as of now demonstrated for CML (imatinib, dasatinib, and nilotinib), yet is most usually observed with dasatinib. Late information from imatinib safe patients accepting dasatinib at a substantial malignancy focus demonstrate that pleural effusion happen in up to 35% of patients, with chance continuing after some time. Pleural effusion may develop suddenly and as late as two years into treatment with couple of prescient elements. These effusions can prompt different difficulties and require extra restorative asset utilize past the common routine care. A few hazard factors for dasatinib-related pleural effusion have been accounted for.[6]

In view of multivariate examinations from a few informational indexes, detailed hazard factors for the advancement of pleural effusion incorporate history of cardiac disease, hypertension, hyper cholesterolemia, immune system sickness, and skin rash amid/preceding imatinib or dasatinib treatment and a twice-every day dasatinib plan.[7] Further, these occasions happen all the more every now and again in older patients. This study was undertaken to analyse pleural effusions in patients with chronic myelogenous leukemia post-imatinib failure.

MATERIALS AND METHODS:

Total 270 patients, who have experienced treatment failure with imatinib therapy because of hematologic/ cytogenetic resistance or intolerance were randomly assigned to dasatinib 100 mg once daily, 50 mg twice daily, 140 mg once daily, or 70 mg twice daily. Treatment was regulated until convention characterized malady movement or passing, unsatisfactory harmfulness, or patient/agent demand to stop treatment. Study was endorsed by the institutional audit board. All patients gave composed educated assent before contemplate passage.

CBCs and serum assessments were performed week after week for 12 weeks, at that point each other week for 3 months, at that point at regular intervals. All patients experienced an ECG and chest x-ray (CXR) before beginning dasatinib. A rehash CXR,with or without chest computed tomography (CT) check, was acquired within the sight of dyspnea, chest torment, or respiratory manifestations. Patients with pleural effusion grade 2 or more were assessed by a pneumologist.

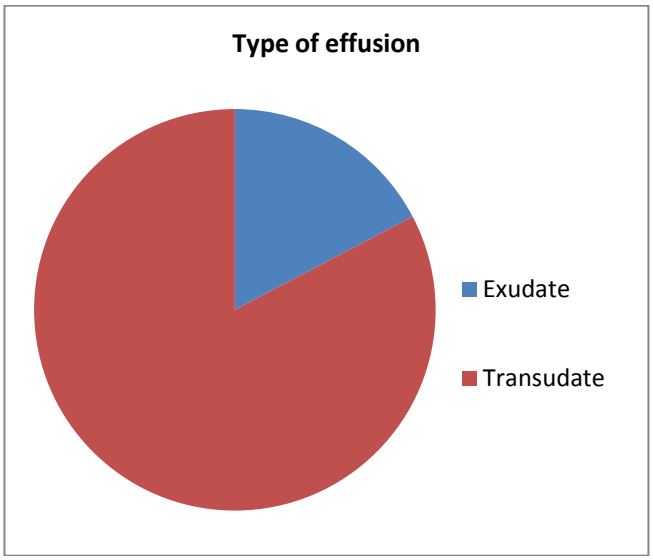
Radiology contemplates were inspected freely by two radiologists. The radiographic degree of pleural effusion was ordered by the greatest volume of effusion including a solitary hemithorax. On the off chance that the span of the pleural effusion is steady with symptomatic change, a CXR can be rehashed roughly every 3months for the primary year, and each 6months for the second year. In the event that the size of the pleural effusion increments, or if indications hold on, intensify, or are unbalanced to the measure of pleural effusion, the patient ought to be alluded to a pulmonologist, in a perfect world one with encounter overseeing patients with dasatinib-related pleural effusions. It is vital to decide if factors (eg, contaminations, cardiovascular comorbidities) other than dasatinib treatment are the reason for an intensifying pleural effusion or a contributing component to indications, especially if a patient is encountering disproportionate symptoms.

RESULTS:

Pleural effusion happened in 32 patients, including 24% of those treated in chronic stage (CP), 46% in accelerated stage (AP), and 29% in blast stage (BP).

Table 1: Demographic details

Variables	Number
Age (years)	35.5 ±7.8
Gender	
Male	189
Female	101
Medical history	
Heart disease	27
Hypertension	41
Hypercholesterolemia	18
Autoimmune disease	12
On imatinib (months)	37
Reason for imatinib discontinuation	68%
Resistance	32%
Intolerance	
Having disatinib (since months)	18
Daily dose mg/d	
140 Once daily	60
70 Twice daily	83
100 Once daily	51
50 Twice daily	76
Time to occur pleural effusion (months)	11
Incidence of pleural effusion	11.85%
Reason of disatinib discontinuation	43
Disease progression	29
Drug toxicity	18
Patient request	
Pleural effusion	
Unilateral	7
Bilateral	25



By examination, history of heart illness, hypertension, and utilization of a twice-every day plan were recognized as variables related with occurrence of pleural effusions. Effusions were exudative in 67% of the assessable cases. In a few patients, effusions were related with reversible additions of right ventricular systolic pressure.

DISCUSSION:

CML constitutes the first disease in which better knowledge of the underlying molecular pathogenesis led to the development of a specific targeted therapy in the form of imatinib. Long-term follow-up data from clinical studies testing imatinib in CML-CP identified a group of patients with CML that does not profit sufficiently from this tailored inhibitor due to primary or secondary resistance to imatinib or intolerance because of adverse effects.[8] Dasatinib displays more potent suppressive activity against wild-type BCR-ABL than imatinib and was approved for the second-line treatment of CML-CP in patients intolerant or resistant to imatinib. The long-term data presented in this review confirm the notion that dasatinib exhibits durable efficacy in CML-CP after imatinib failure, while maintaining a relatively safe toxicity profile, with adverse events being mostly of grade 1 or 2. Dasatinib led to a rapid and deep hematological, cytological, and molecular response in both first- and second-line treatment of CML-CP.[9] Response rates at 3 and 6 months after treatment initiation are being increasingly recognized as predictive markers for low transformation rates into accelerated or blast phases, translating into better long-term outcome and survival.

Findings indicate that a consistent subgroup of CML patients resistant to or intolerant of imatinib can have a long-term benefit from dasatinib therapy. In particular, those with faster and deeper responses to dasatinib are more likely to have better long-term outcomes. Some patients had been treated with imatinib for a prolonged period despite resistance because there were no other options at the time, and such pretreatment could have possibly rendered the diseasemore resistant.[10] After discontinuing study treatment, patients may have resumed treatment with commercially available dasatinib or another BCR-ABL inhibitor, although this information was not available for this analysis.

The mechanism by which dasatinib induces a pleural effusion associated with dasatinib is unclear. It has been suggested that inhibition of PDGFRB, which is expressed in pericytes and is involved in the regulation of angiogenesis, may be implicated (Jayson et al, 2005; Quintas-Cardama et al, 2007).[11,12] However other mechanisms have been suggested. Bergeron et al (2002, 2007) suggested a possible immune-mediated mechanism based on the high lymphocyte frequency in pleural fluids and pleural tissue in those patients, the presence of auto-antibodies reported in one patient and the response to steroids.[13] Our results support a possible immune origin, as the effusions seemed to be associated with other immune-mediated reactions, such as skin rash on imatinib or dasatinib or prior history of auto-immunity.

We investigated the impact of several variables on the development of pleural effusion. Blastic phase CML, previous history of cardiac disease, hypertension and hypercholesterolemia were significantly associated with an increased risk of pleural effusion.[14,15] Our findings are consistent with a recent published study (Quintas-Cardama et al, 2007), where a higher incidence of pleural effusions was seen in patients with hypertension, a history of cardiac disease and a dasatinib dosage >100 mg per day. Because an immune mediated mechanism has been suggested as a possible explanation for pleural effusion under dasatinib (Bergeron et al, 2007)[13], we investigated different immune-mediated events among those patients. Interestingly 11 patients had a previous history of auto-immune disease.

By multivariate analysis, prior cardiac history, hypertension, and twice-a-day administration of dasatinib were associated with an increased risk of pleural effusion. The importance of the latter factor is supported by recently published studies comparing daily versus twice daily dasatinib schedules.[16,17] In CP, patients treated with 100 mg once daily had lower incidence of pleural effusion compared with those treated with 50mg bid, 140mg once daily, or 70mg bid. After the effusion has resolved, dasatinib can be resumed at a reduced dose. With adequate management, most patients continue therapy and have the opportunity to achieve the antileukemic effect reported with dasatinib.

CONCLUSION:

Pleural effusion is a complication of dasatinib therapy in CML. This occurrence is usually mild or moderate and more frequent among patients in advanced CML phases and in those treated

at daily doses of 140 mg or higher, particularly when administered on a twice-daily schedule. With adequate management, most patients can continue therapy with

dasatinib. Further studies are needed to elucidate the pathophysiology of this complication.

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