Review

Pleural Effusion in Dasatinib-Treated Patients With Chronic Myeloid Leukemia in Chronic Phase: Identification and Management

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Abstract

Dasatinib has demonstrated durable clinical responses in patients, both as first-line and subsequent lines of therapy. Dasatinib use can result in pleural effusion in some patients, occurring any time during treatment and commonly characterized as mild to moderate in severity. Early identification of symptoms is essential in the proper management of pleural effusion. Prompt confirmation of diagnosis and management of pleural effusion can minimize morbidity and maximize the ability to preserve long-term clinical benefits with dasatinib. Here, we provide guidance on early identification and management of dasatinib-related pleural effusion.

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Introduction

With the advent of BCR-ABL1 tyrosine kinase inhibitors (TKIs), chronic myeloid leukemia (CML) is now a manageable disease with the possibility of near-normal life expectancy.[1] Dasatinib, a second-generation TKI, has proven to be effective for the long-term treatment of CML, both as initial and subsequent lines of therapy.[2,3] Durable efficacy, including high rates of major molecular response, progression-free survival, and overall survival, has been reported with long-term follow-up of dasatinib in CA180-034, a phase III dose-optimization trial that evaluated 4 dasatinib dosing regimens (50 mg twice a day [b.i.d.], 100 mg once daily [q.d.], 70 mg b.i.d., 140 mg q.d.) in imatinib-resistant or -intolerant patients with CML in chronic phase (CML-CP; n = 670), as well as in DASISION (DASatinib versus Imatinib Study In treatment-Naive CML patients; CA180-056), a phase III trial that assessed first-line imatinib (400 mg q.d.) versus dasatinib (100 mg q.d.) in newly diagnosed patients with CML-CP (n = 519).[2,3]

Pleural effusion is an adverse event that has been reported more commonly with dasatinib than with other TKIs in patients with leukemia.[4] With a minimum of 5 years of follow-up in DASISION, 28% of dasatinib-treated patients with CML-CP had drug-related pleural effusion of any grade (3% with grade 3/4; Table 1) compared with 1% of imatinib-treated patients.[2] In the study CA180-034, drug-related pleural effusion of any grade occurred in 33% of patients overall (Table 1) and in 28% of patients treated with the standard 100 mg q.d. dose, with a minimum of 7 years follow-up.[3]

With adequate clinical management (including dose interruptions, dose reductions, and pharmacologic interventions) discontinuation of dasatinib owing to the related pleural effusions was necessary in a minority of patients with CML-CP in both the DASISION and the CA180-034 studies. During the 5-year follow-up period in DASISION, 6% of dasatinib-treated patients discontinued therapy owing to drug-related pleural effusion of any grade.[2] Similarly, during the 7-year follow-up period in CA180-034, 7% of patients treated with the approved 100 mg q.d. dose discontinued treatment owing to drug-related pleural effusion of any grade (2% with grade 3/4).[3]

Although the mechanism of dasatinib-related pleural effusion is not clearly understood, it has been speculated that this adverse event may be immune-mediated, based on reports of high lymphocyte counts, often

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Table 1 Summary of PE in Dasatinib-Treated Patients

	Dasatinib-Treated Patients, N (%)	
	DASISION (N = 258)	CA180-034 (N = 662)
Patients with PE (any grade)	74 (28.7)	227 (34.3)
Patients with drug-related PE (any grade)	73 (28.3)	220 (33.2)
Patients with grade 3/4 PE	7 (2.7)	48 (7.3)
During 1st year	NA	15 (2.3)
During 2nd year	NA	9 (1.4)
During 3rd year	3 (1.2)	9 (1.4)
During 4th year	1 (0.4)	2 (0.3)
During 5th year	2 (0.8)	4 (0.6)
During 6th year	1 (0.4)	4 (0.6)
After 6 years	NA	5 (0.8)
Patients with >1 drug-related PE (any grade)	45 (17.4)	134 (20.2)
Median time to first drug-related PE, weeks (range)		
Any grade	113.6 (3.9-298.6)	60.1 (0.6-371.1)
Grade 1/2	113.6 (3.9-298.6)	63.9 (0.6-371.1)
Grade 3/4	174.9 (114.0-273.7)	102.4 (1.9-350.4)
Duration of first drug-related PE (any grade), weeks (range)	3.7 (0.1-223.4)	3.6 (0.3-235.4)

Abbreviations: NA = not applicable; PE = pleural effusion.

of a natural killer cell phenotype, in pleural fluid and tissue.[5-8] A study conducted by Mustjoki and colleagues reported that patients with leukemia who experienced lymphocytosis during dasatinib therapy had higher rates of pleural effusion; of note, this was also associated with improved response rates.[9] Alternatively, dasatinib-related pleural effusion may occur through potent inhibition of the platelet-derived growth factor receptor β, leading to a reduction in interstitial fluid pressure, or inhibition of SRC-family kinases, resulting in vascular permeability changes.[6] The mechanism for the development of lymphocytosis and the reason why other TKIs with inhibitory activity against platelet-derived growth factor receptor β induce pleural effusion at much lower frequencies remain unknown.

Several risk factors for dasatinib-related pleural effusion have been reported. Based on multivariate analyses from several data sets, reported risk factors for the development of pleural effusion include history of cardiac disease, hypertension, hypercholesterolemia, autoimmune disease, and skin rash during/prior to imatinib or dasatinib treatment and a twice-daily dasatinib schedule.[6,7] Further, these events occur more frequently in older patients.[10]

Pleural effusion can occur at any time during treatment with dasatinib (Table 1).[2,3] In DASISION, the median time to first grade 1/2 pleural effusion was 114 weeks (range, 4-299 weeks).[2] New cases of pleural effusion occurred in 5% of patients at risk treated with dasatinib 100 mg q.d. compared with 8% in other treatment arms within year 7 of CA180-034.[3] Therefore, patients with pleural effusion would likely benefit most from a coordinated effort in adverse event management between oncologist and pulmonologist. Both early identification of symptoms and prompt management of pleural effusion are important to minimize morbidity from the event and disruptions to dasatinib treatment in an effort to optimize the potential clinical benefit of therapy.

Currently, there is a scarcity of general guidelines for the management of dasatinib-associated pleural effusion, and no prospective trials of intervention strategies for dasatinib-associated pleural effusion are in progress or planned. Here, we present some suggested management strategies for the early identification and management of pleural effusions in dasatinib-treated patients with CML, from a team of oncology and pulmonary medicine physicians with ample experience managing these complications.

Identifying and Diagnosing Pleural Effusion

Common symptoms of pleural effusion include dyspnea, dry persistent cough, and chest tightness (Figure 1). Additionally, patients may have decreased exercise tolerance and constitutional symptoms, such as fatigue. A chest x ray (CXR) or ultrasound is recommended once the clinical suspicion of pleural effusion is established. A thorough medical history and physical exam remain crucial to investigate non–drug-related causes of the symptoms suggestive of pleural effusion (eg, infections and cardiovascular conditions). In particular, when a patient has dyspnea along with a negative CXR, the clinician should suspect pulmonary arterial hypertension, and perform the appropriate diagnostic procedures to confirm, then implement proper management if warranted.

Pleural effusions are categorized as small, medium (moderate), or large, based on the volume of the pleural effusion observed by CXR at the time of diagnosis. In general, small effusions (< 500 mL) are seen as blunting of the costophrenic angles. Of note, costophrenic angle blunting is not specific for pleural fluid and may be a result of pleural thickening; thus, further radiographic investigation with decubitus films, ultrasound, or computed tomography (CT) imaging may be required to confirm the presence of a pleural effusion or reveal other suspected conditions. Pleural effusions that are beyond the blunting of the costophrenic angle (extending to the hilum) are considered medium. Effusions that occupy more than 30% to 50% of the hemithorax and are above the hilum are considered large.[11] Characteristics and sizing of pleural effusions have been described in previous literature.[12-14] Notably, this clinical categorization of pleural effusion varies from the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 definition used to report adverse events in clinical trials, which classifies pleural effusion based on the severity of the symptoms and requires intervention using a grading scale of 1 to 5, with 1 as asymptomatic (no intervention indicated) and 5 as death associated with the adverse event.[15]

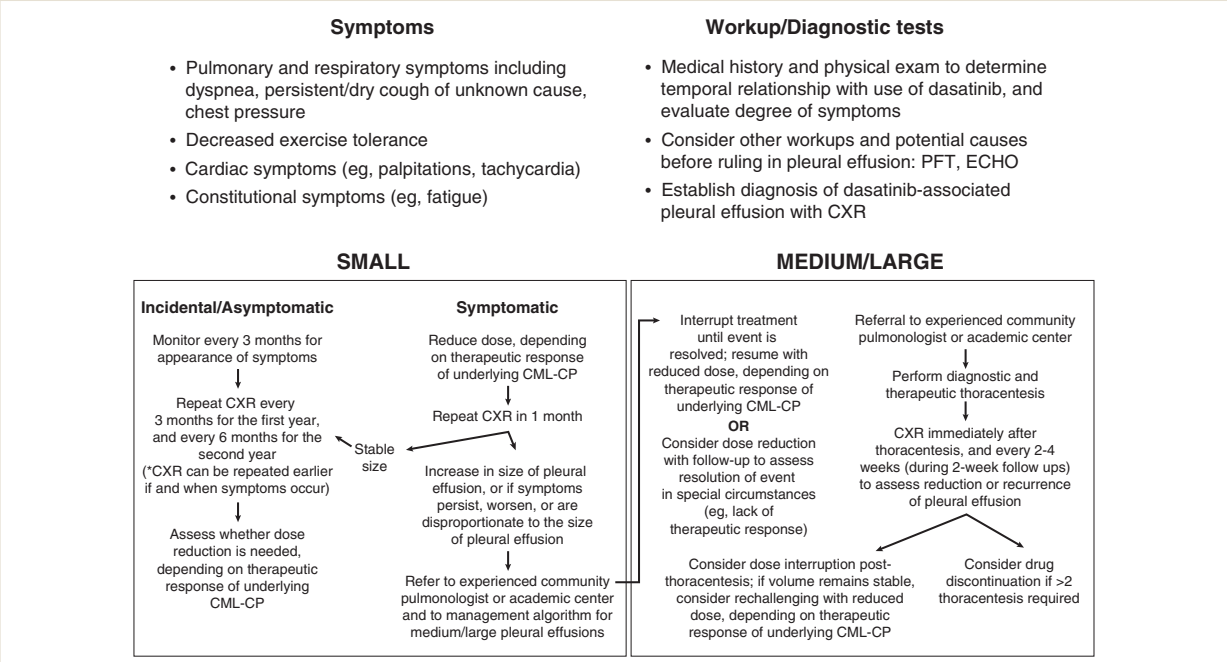
Algorithm for the Management of Dasatinib-Associated Pleural Effusion

Management of pleural effusion is dependent on the size of the pleural effusion and the symptoms associated with it. A suggested algorithm on management of dasatinib-related pleural effusion, based on our experience and reports from the literature, is shown in Figure 1.

Management of Small Pleural Effusions

Incidental/Asymptomatic. Patients with asymptomatic pleural effusion of small volume should be monitored regularly for

Figure 1 Identification and Management Algorithm for Dasatinib-Associated Pleural Effusion. A Schema for Diagnostic Workup and Management of Dasatinib-Associated Pleural Effusions, Grouped by Effusion Volume



Abbreviations: CML-CP = chronic myeloid leukemia in chronic phase; CXR = chest x ray; ECHO = echocardiogram; PFT = pulmonary function test.

appearance of symptoms, and a follow-up CXR should be repeated approximately every 3 to 6 months for the first year, and every 6 months for the following year. Importantly, a follow-up CXR should be repeated earlier should any symptoms occur or worsen. The dasatinib dose may be reduced based on therapeutic response of the underlying CML-CP.

Symptomatic. For patients with symptomatic pleural effusion of small volume, a CXR is recommended and follow-up is required (eg, 1 month later), to monitor the volume of the effusion and correlate the image with clinical symptoms. Temporary treatment interruption should be considered in patients with significant symptomatology or those with risk factors (eg, older age, pulmonary or cardiac comorbidities, a history of autoimmune disease) suggestive of greater adverse event intensity or associated morbidity. Once effusion resolves or improves significantly, treatment may be resumed, and a dose reduction is usually recommended. The magnitude of the dose reduction varies according to the response of CML to therapy, the presenting symptoms, whether the effusion is recurrent, and the patient's risk factors. A modest (ie, 20%) dose reduction is adequate in most instances (eg, from 100 mg to 80 mg). However, for patients at increased risk, larger dose reductions can be considered (ie, 50%), particularly in patients already experiencing stable molecular response to therapy. Occasionally, dose reductions may be implemented without treatment interruptions, particularly if response to therapy is inadequate (eg, no hematologic response). However, transient treatment interruptions accompanied by medical management, followed by resumption at a lower dose may help expedite recovery and improve odds of complete resolution. If the response to therapy is inadequate (eg, treatment failure by European LeukemiaNet guidelines or prolonged suboptimal response) or suffers greatly as a result of therapy interruption/dose reduction, change to a different TKI should be strongly considered.[16,17]

It should be noted that small volume effusions are likely to be asymptomatic. If symptoms such as dyspnea are present with a small volume effusion, one should look for causes of the dyspnea other than the effusion. The CXR should be repeated 1 month later, then 3 and 6 months following. If the size of the pleural effusion is stable with symptomatic improvement, a CXR can be repeated approximately every 3 months for the first year, and every 6 months for the second year.

If the size of the pleural effusion increases, or if symptoms persist, worsen, or are disproportionate to the size of pleural effusion, the patient should be referred to a pulmonologist, ideally one with experience managing patients with dasatinib-associated pleural effusions. It is important to determine whether factors (eg, infections, cardiovascular comorbidities) other than dasatinib therapy are the cause of a worsening pleural effusion or a contributing factor to symptoms, particularly if a patient is experiencing disproportionate symptoms.

It may be useful to perform an echocardiogram on patients who develop pleural effusion. This can not only identify other conditions that may predispose to pleural effusion, but may also help identify pulmonary hypertension, a complication that has been reported in some patients treated with dasatinib. Patients with pleural effusion associated with dasatinib have been reported to frequently have increased right pulmonary pressures by

echocardiogram.[6] Such findings may require additional investigation, including pulmonary artery (right heart) catheterization for definitive screening for pulmonary hypertension, and may further support the need for a transient treatment interruption or permanent discontinuation.

Management Modalities. Diuretics have been used to manage pleural effusion in some instances. Diuretics may be particularly effective in managing pleural effusion when associated with certain conditions (eg, volume overload, congestive heart failure), but their benefit is more questionable in managing effusion associated with other etiologies (eg, inflammatory).

The use of corticosteroids to treat dasatinib-associated pleural effusions was allowed during clinical trials, and their use is included in the dasatinib label; however, no interventional trial based on mechanism of action has been offered and thus a consensus regarding the use of corticosteroids has not been reached. A short course of corticosteroids can be attempted in some instances, but sustained use of corticosteroids for the purpose of managing pleural effusions is not recommended.

If pleural effusions are diagnosed early enough, they should be managed pharmacologically; small pleural effusions will rarely, if ever, require thoracentesis if managed promptly and properly.

Management of Medium to Large Pleural Diffusions

For medium or large pleural effusions, dasatinib therapy should be temporarily stopped until the adverse event is resolved, and then resumed at lower doses.[18] Reducing the dose of dasatinib without interruption is not generally optimal for the management of dasatinib-associated effusions. However, in occasional instances where rapid control of the disease is considered critical (eg, when patients have not yet achieved a hematologic response), clinicians may consider continuing dasatinib at a reduced dose, with close follow-up to assess resolution of the event. Regardless of approach, the goal remains to maintain the clinical response when possible.

In some instances, a patient with a medium or large pleural effusion may require therapeutic thoracentesis; the patient should be referred to an experienced pulmonologist or an academic center. In patients with persistent effusions and accompanying symptoms,[19] other processes should be ruled out (eg, infection, congestive heart failure, liver failure). If thoracentesis is performed, then measurements of total protein, lactate dehydrogenase, cell count with differential, cytology, and microbiology can and should be obtained, to determine the origin of the effusion.[19] If pleural fluid is bloody, fluid hematocrit should be measured. If it is milky in appearance, fluid triglycerides and cholesterol should be obtained as well. Dasatinib-associated pleural effusions are usually exudative by the Light criteria[19] but may be transudative if congestive heart failure, cirrhosis, or nephrotic syndrome is present concurrently. The effusion typically predominantly lymphocytes ($\geq$ 70% lymphocytes). Hemorrhagic and chylous effusions attributed to dasatinib have been described but are relatively uncommon.[20] CXR should be performed immediately after thoracentesis and repeated every 2 to 4 weeks until the effusion resolves, or becomes stable, or does not recur for 2 to 3 months, to determine the amount of pleural effusion reduction, as well as establish a baseline for comparison in future follow-up. For patients who interrupt dasatinib, it is appropriate to repeat CXR at least once after 2 to 4 weeks to monitor any evidence of progression. For patients requiring thoracentesis, a temporary post-procedure treatment interruption should be considered. Once the pleural effusion has resolved, the algorithm for small pleural effusion management may be followed for monitoring. If pleural effusion recurs and requires more than 2 thoracentesis procedures, particularly within a short time frame (ie, every 2 weeks), physicians should consider permanently discontinuing drug and changing therapy.

Patients with recurrent pleural effusion requiring repeated thoracentesis should discontinue dasatinib. For patients with recurrent pleural effusions in whom dasatinib is considered the only viable alternative for the management of CML, an option may be management with an indwelling pleural catheter or, in rare instances, pleurodesis.

Diuretics can be used to manage these larger effusions; however, the use of diuretics or steroids is perhaps less likely to be effective in patients with moderate or large pleural effusions. The mechanism of action and benefit of these therapies is not firmly established, and their clinical efficacy may be limited. In some instances, diuretics and corticosteroids may be used after thoracentesis to minimize the probability of recurrence. However, the clinical value of this practice has not been established, and routine use is not supported in this setting, unless there are contributing or comorbid factors that would improve from such interventions, such as concomitant congestive heart failure.

Conclusions

Although dasatinib has demonstrated long-term efficacy in patients with CML,[2,3] its use is also associated with an increased frequency of pleural effusion compared with other BCR-ABL1 TKIs. The majority of pleural effusions with dasatinib were mild to moderate. Early identification of symptoms and tailored management of pleural effusion are essential in optimizing clinical outcomes and safety with dasatinib. In patients who develop symptoms of pleural effusion, assessment of response to therapy and investigation of other potential patient factors are necessary before deciding an appropriate course of action. Management of dasatinib-induced pleural effusion may include dose interruptions, dose reductions, or permanent discontinuation. The role of diuretics and steroids in the management of dasatinib-related pleural effusions, although commonly used for this purpose, is unclear, and studies to elucidate their clinical benefit are needed. Patients with effectively managed pleural effusions have been shown to achieve clinical responses to dasatinib, and may continue to gain long-term benefits with dasatinib treatment.

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