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Guidelines for the management of pleural effusions during dasatinib treatment in chronic myeloid leukemia

Massimo Breccia[1], Luigiana Luciano[2], Alessandra Iurlo[3], Fabio Stagno[4], Matteo Molica[1], Antonella Gozzini[5], Giuseppe Saglio[6], Giuliana Alimena[1]

[1] Department of Cellular Biotechnologies and Hematology, Sapienza University, Rome, Italy; [2] Hematology, University "Federico II", Naples; Italy; [3] Hematology, Fondazione Cà Granda, Policlinico of Milan, Italy; [4] Hematology, Ospedale Ferrarotto, University of Catania, Italy; [5] Hematology, University of Florence, Italy; [6] Division of Hematology and Internal Medicine, Department of Clinical and Biological Sciences of the University of Turin, Orbassano, Italy

Summary. Dasatinib is indicated for chronic myeloid leukemia (CML) patients with resistance or intolerance to imatinib or as a first line therapy in chronic or blastic phase of the disease; it has 325-fold increase potency compared to imatinib and is active in mutated and unmutated resistant patients. Pleural effusions are therapy-related events that can occur in all subset of patients treated with this drug. Aim of this paper is to draw up clinical guidelines on the management of pleural effusions associated with dasatinib treatment. Recommendations are based upon the published data and clinical personal experience from a number of different centres. Incidence of pleural effusions in different dasatinib trials, the related pathogenetic mechanisms and the associated risk factors are discussed. Practical recommendations to manage pleural effusions were finally composed. Adequate monitoring of patients with predisposing factors is necessary in order to early identify subjects at risk of developing such complications as well as to correctly manage them.

Key words: dasatinib, chronic myeloid leukemia, pleural effusions, management, risk factors

«Linee guida per la gestione dei versamenti pleurici durante il trattamento con dasatinib nella leucemia mieloide cronica»

Riassunto. Dasatinib è indicato in pazienti con leucemia mieloide cronica (LMC) con resistenza o intolleranza ad imatinib o come terapia di prima linea in fase cronica o blastica della malattia; è 325 volte più potente confrontato con imatinib ed è attivo in pazienti resistenti mutati e non mutati. Il versamento pleurico è un effetto collaterale-terapia correlato che può verificarsi in tutti i sottogruppi di pazienti trattati con questo farmaco. Scopo di questo lavoro è quello di elaborare linee guida cliniche per la gestione dei versamenti pleurici associati al trattamento con dasatinib. Le raccomandazioni sono basate su dati pubblicati e su esperienze cliniche personali provenienti da un certo numero di centri diversi. Sono stati discussi l'incidenza di versamenti pleurici in diversi trial con dasatinib, i relativi meccanismi patogenetici e i fattori di rischio associati. Alla fine sono state preparate le raccomandazioni pratiche per gestire i versamenti pleurici. È necessario un adeguato monitoraggio di pazienti con fattori predisponenti per identificare tempestivamente soggetti a rischio di sviluppare tali complicanze così come per gestirle correttamente.

Parole chiave: dasatinib, leucemia mieloide cronica, versamenti pleurici, gestione, fattori di rischio

Introduction

Dasatinib as second or first line therapy

Dasatinib is an oral dual tyrosine kinase inhibitor active against abl and Src-family kinases: it was approved by the US Food and Drug Administration (FDA) for the treatment of chronic myeloid leukemia (CML) patients in chronic (CP), accelerated (AP), or blast phase (BP) with resistance or intolerance to imatinib therapy, and is also indicated for the treatment of adults subjects with Ph^+ ALL who have become resistant or intolerant to other treatments (1). It has also been approved for the treatment of newly diagnosed CML patients in CP. It inhibits *BCR–ABL1* with a 50% inhibitory concentration (IC50) of <1 nmol/L and is also active against *c-KIT, PDGFR*, and *EPHA2*, as well as against members of Src kinase family, such as Lyn, Yes, and Src, with an IC50 of 0.5 nmol/L (2). The structure of dasatinib is based on a different chemical scaffold to imatinib and has a 325-fold greater potency obtained in "in vitro" experiments against the BCR-ABL target. It binds both the inactive and the active conformations of the ABL kinase domain. Dasatinib is active against all *BCR–ABL1* mutations conferring imatinib-resistance that have been tested to date, except for the T315I mutation (3-7).

Several studies tested the efficacy and safety of dasatinib as second line therapy. START-C trial (8, 9) tested dasatinib (70 mg BID) in 387 patients with resistance (75%) or intolerance (25%) to imatinib. Complete hematologic remission (CHR) was achieved by 90% of patients; major cytogenetic response (MCyR) was obtained in 62% of patients and was maintained in 88% of these patients at 24 months. Complete cytogenetic response (CCyR) rate was 53% and this response was maintained in 90% of patients at 24 months. PFS at 2 years was 80% and 2-year OS was 94%. Mutations of the kinase domain were detected at baseline in 44% of enrolled patients, with increased frequency of G250E and T315I mutations. The presence of mutations at baseline, even if located in the p-loop region, did not influence overall response rate. Branford and colleagues reported on the development of new mutations in 479 patients treated with dasatinib in this trial: new mutations, such as T315A, F317L, V299L, E255, occurred in only 13% of treated patients and in particular some, such as F317L, showed resistance to the drug (10, 11).

Dasatinib was tested in advanced phase of disease: START-A trial recruited 174 AP CML patients, the majority of whom resistant to imatinib that were treated with dasatinib 70 mg BID. Major hematologic response (MaHR) and CHR were achieved in 64% and 45% of patients. MCyR and CCyR were obtained in 39% and 32% of patients, with PFS and OS being 66% and 82% at a median follow-up of 1 year (12). Dasatinib was tested also in BP-CML (START-B) which showed CCyR rates ranging from 27% to 43% and in Ph+ acute lymphoblastic leukemia (ALL, START-L trial) reported the results obtained in 36 patients with overall CCyR rate at 8-month follow-up of 58%. No differences in response rates were revealed for patients with resistant mutations compared to whole non-mutated population (13, 14).

CA180-034 study was an international, open-label, four-arm randomized phase III study, which enrolled 662 patients resistant or intolerant to prior imatinib therapy. Patients received dasatinib at doses of 140 mg or 100 mg, both administered in QD or BID schedule (15). Baseline features as well as outcomes at 72 months were similar among the different arms. CHR was achieved in 92% of the 100 mg QD arm, whereas CCyR was achieved in 50% and 53% of the 100 mg QD and 70 mg BID arms, respectively. MMR rate was 45% in the 100 mg QD cohort at the last follow-up of 72 months. OS was estimated to be 71% in the 100 mg QD arm with a cumulative incidence of death due to CML of 12.5%. PFS in the 100 mg QD arm was estimated to be 49% at 6 years.

A subsequent phase 3 study assessed safety and efficacy of two different schedules of dasatinib (140 mg QD or 70 mg BID) in patients with myeloid or lymphoid BP. A two-year follow-up showed that MaHRs were similar in MBP treated with the two different schedules (28%), whereas for LBP the response rate was 42% for 140 mg QD and 32% for 70 mg BID. MCyR rate was 25% for 140 mg QD and 28% for 70 mg BID in MBP patients while respective rates for LBP were 50% and 40%. Two-year OS with 140 mg QD and with 70 mg BID was 24% and 28% in MBP patients, and 21% and 16% in LBP, respectively. In this

trial a trend of better tolerability was reported among patients treated with 140 mg QD (16).

The phase III DASISION trial enrolled 519 patients in CP that were randomized to dasatinib 100 mg QD or imatinib 400 mg. The results after 5 years of follow-up showed that major molecular response (ratio BCR/ABL ≤ 0.1% or MMR) was achieved in 76% of patients treated with dasatinib and in 64% of patients treated with imatinib. Molecular responses were achieved independently from Hasford risk at baseline. The cumulative rates of MR4.5 (ratio BCR/ABL ≤ 0.0032%) were 42% with dasatinib, and 33% with imatinib, respectively. The rate of transformation to AP/BP at 5 years was 4.6% with dasatinib and 7.3% with imatinib (17).

Frequency of pleural effusions in different trials

Pleural effusions can be classified according to CTC scale as grade 1 when not symptomatic and that did not require treatment, grade 2 for symptomatic patients requiring diuretics, grade 3 as requiring oxygen therapy or therapeutic thoracentesis and grade 4 for life-threating conditions requiring intubation. Usually pleural effusions cause no symptoms and these are more likely when effusion is moderate or large, including shortness of breath, chest pain, fever and cough. Pleural effusions are quiet specific to dasatinib treatment since these adverse events are very rare with all other inhibitors. In a dasatinib phase I trial published in 2006, pleural effusions were reported in 13% to 35% of patients, particularly among those treated in AP or BC, with grade 3/4 occurring in 0% of patients in CP and in 13% of patients in myeloid BC (18). In the START-C study, the incidence of pleural effusion was 19%: it was of grade 1/2 during the first year with a slight increase to 25% at the follow-up of two years; grade 3 pleural effusions were recorded in less than 10% of patients and no grade 4 events were observed (8,9, table 1).

In the START-A trial, pleural effusions occurred in 27% of patients but were of grade 3/4 in only 8 patients (5%) with none of this requiring discontinuation of therapy (12). In the phase III trial for CP patients comparing four different dasatinib schedules, the overall rate of the adverse event slightly increased from 10.3% to 13.9% between the first and the second year of follow-up, with only 2.4% being of grade 3 and none of grade 4. The occurrence of effusions of all grades was 14% in the 100 mg QD arm compared to 25% in the 70 mg BID arm (p=0.021). The 36-month follow-up confirmed a slight increase of all grades pleural effusion, between 24 and 36-months of treatment. No adverse outcome was observed for patients who developed pleural effusions: across all study arms, patients with or without pleural effusion demonstrated similar PFS and OS, and cytogenetic response rates were higher in patients with the pleural complication (19,20).

In the phase III trial for advanced disease phase, the incidence of pleural effusions (all grades) in AP patients was 20% in the 140 mg QD arm compared to 39% in the 70 mg BID arm. For myeloid BC, it was 20% while, in lymphoid BC, it was 21% versus 36% in patients treated with 140 mg QD or 70 mg BID respectively (16).

MD Anderson Cancer Center tested dasatinib at the dose of 100 mg/day in 62 previously untreated CP-CML patients. Pleural effusions showed an incidence

Table 1. Prevalence of pleural effusion in reported studies.

Reference	Study	Prevalence of pleural effusion
(18)	Phase I	13-35% (grade 3/4 13%)
(8,9)	START-C	25% (grade 3 6%, no grade 4)
(12)	START-A	27% (grade 3/4 5%)
(19,20)	Phase III (study 034)	25% (at 6 years)
(16)	Phase III (study 035)	20% (for BP pts with 140 mg QD)
(21, 22)	MDACC firstline	13% (grade 3/4 2%)
(17)	DASISION	24% (at 4 years)

of 13% in evaluable patients, with 2% being of grade 3-4. Half of the enrolled patients were treated with 100 mg once daily whereas the other half received 50 mg twice daily: there was a trend of lower incidence of pleural events in patients treated with 100 mg once daily (3% vs 10%) (21,22).

In the DASISION trial, cumulative incidence of effusions of all grades was 10%, 14.3%, 19% at 1, 2 and 3 years respectively; at last follow up of 5-year presented, was 28% in the dasatinib arm vs 0.4% recorded in patients receiving imatinib (17).

Pleural effusions were usually exudates and were not related to fluid retention, unlike those previously described with imatinib; fluid analysis showed mostly lymphocytic accumulation and lung manifestations were frequently found associated to effusions (23).

Pathogenesis and potential risk factors associated to pleural effusions

One of the first observations relating potential risk factors for pleural effusions was reported by Quintas-Cardama et al (24): in a series of 138 patients treated with dasatinib at different doses and schedules from MD Anderson Cancer Center. Thirty-five percent of patients experienced pleural effusions, that were of grade 3/4 in 11 patients (23%) and asymptomatic in 13 patients. Median time from start of therapy to diagnosis of effusion was 5 weeks. History of previous or concomitant cardiac disease, hypertension and BID schedule were identified as predisposing risk factors, whereas advanced disease phase was significant only by univariate analysis. The authors suggested that potential pathogenetic mechanism(s) consisted in inhibition of *PDGFR*-β that is expressed in pericytes and is involved in the regulation of angiogenesis; the inhibition of Yes and Src kinases which are involved in the stability of pleural epithelium through regulation of cell adhesion; dasatinib-induced pulmonary hypertension (PAH), which was initially observed in a small series of patients presenting PAH and concomitant pleural effusion.

The Hammermisth group reported 62 patients treated with dasatinib, of whom 17 (27%) experienced pleural effusion, with a cumulative incidence at 1 year of 29.5%. Median time for occurrence of the event was 5.9 weeks. Potential risk factors associated to effusions were advanced disease phase, previous history of cardiac disease, hypertension and hypercholesterolemia, probably this last as result of statistical bias. The authors identified also that a previous history of autoimmune disorders and skin rashes experienced during imatinib therapy were significant factors associated to effusions. Different pathogenetic mechanisms were suggested: inhibition of *PDGFR*-β or possible immune-mediated effects, hypothesized on the basis of high lymphocyte count found in the pleural fluids (25).

When dasatinib was tested as second line after imatinib failure, risk factors associated to effusions were only the older age (>66 years) with an odd ratio of 8.2%, whereas other factors, such as prior stem cell transplantation, male sex, longer time interval from diagnosis, were associated to a decreased risk. In the 034 study, lymphocytosis was observed in 37% of patients who developed pleural effusion compared to 26% of patients without this complication (20).

The possible role of lymphocytosis observed in patients treated with dasatinib was also described in 22 patients with Ph+ leukemias: it was morphologically recognizable as a large granular lymphocyte (LGL) expansion and phenotypically as a CD8+ T-cytotoxic or oligoclonal NK expansion. Pleural effusions were observed more frequently in patients developing lymphocytosis, cytomegalovirus (CMV) reactivation, fever and colitis. Improvement of OS was also reported in patients with lymphocytosis (26). In a subsequent analysis it was hypothesized that CMV reactivation is intimately linked to LGL expansion in CML patients treated with dasatinib. It is possible that activated lymphocyte may target both leukemic and CMV-infected cells because of epitope sharing but it is still unclear if lymphocytosis has a pathogenetic effect or is a consequence of drug administration (27).

Other groups reported LGL proliferation in CML patients treated with dasatinib: the Austrian group (28) reported on the occurrence of lymphocytosis in 4/15 patients receiving dasatinib. The exact mechanism is not fully explained, but it has been suggested that dasatinib may mediate, through inhibition of Src kinases, LGL proliferation. An LGL count increased has been reported after 2 hours from dasat-

inib intake (29), but the differences with transient and sustained lymphocytosis are still unclear. It has also been reported that dasatinib may induce abnormalities in lymphocyte trafficking through the lung lymphatic network in the majority of exudative effusions (30). The dose of 100 mg QD finally reduce the occurrence of pleural effusions as reported in a retrospective exposure-response analysis of the dose optimization phase III trial: 11% with 100 mg QD as compared to 16.2% with 50 mg BID and 22% with 70 mg BID. Age over 55 years and Cmin were identified as significant risk factors for effusions (31). In a retrospective cooperative analysis including 172 elderly patients treated with dasatinib after imatinib resistance, the incidence of effusions was 30% of grade 3/4 in 8.1% of patients. This side effect was recurrent in 48% of patients and the significant risk factors associated were the concomitant presence of lung diseases and the initial dose of the drug (more frequent in patients treated with high dose) (32).

With the aim of analyzing if comorbidities at baseline may have an influence on pleural effusion development, we retrospectively applied the Charlson comorbidity index (CCI) to a cohort of 83 elderly CP-CML patients receiving dasatinib as a second line. CCI is a list of 19 possible concurrent comorbidities, each one with a prognostic weight. Score point 0 was assigned to 59 patients (71%), whereas a score point >1 was attributed to 31 patients (18 patients =1, 10 patients= 2; 2 patients= 3; 1 patient= 5). Overall, 23 patients (28%) experienced pleural effusion during treatment: 15 of these (65%) had score = 1 and 8 (35%) had score > 1. Seven patients experienced grade 3 and 16 patients grade 1-2 effusions. In patients with high score, the effusions occurred several times and were usually associated to persistent skin toxicity. No pleural effusions were observed in patients with score 0. The results of this study suggested that the presence of comorbidities may correlate with the occurrence of pleural effusions during dasatinib treatment and that patients with higher scores deserve a strict monitoring (33). No conclusive data were reported about grade of effusion relating the severity of underlying cardiologic and pulmonary disease: from a subanalysis of DASISION trial an increased rate of effusions was revealed in patients with pre-existing cardiovascular diseases (34).

Clinical guidelines for the management of pleural effusions

The MD Anderson group referred on the management of 48 cases of pleural effusion (24): they indicated that transient drug interruptions (median of 27 days) were adopted in 40 patients (83%) and drug reduction was requested in 34 patients (71%). Only 7 patients out of 48 received short courses of prednisone: less median time of transient interruption was recorded among the patients who received prednisone compared to median time of patients that were managed without steroids. Nineteen patients with large effusions received diuretic treatment. Nine patients with grade 3 effusions required a therapeutic thoracentesis.

The Hammersmith group reported as management of pleural effusion the discontinuation of dasatinib and treatment with diuretics in all patients; thoracentesis was performed in only 3 patients. Definitive drug discontinuation was performed in 3 patients due to recurrence of effusions (25).

Porkka et al reported on the management of pleural effusions occurring in 23 patients treated with the dose of 100 mg QD in the randomized 034 study: 12 patients required temporarily discontinuation (followed by dose reduction in 8 patients), 13 patients received diuretics, 6 patients were treated with steroids. Thoracentesis was performed in 12 patients across all the randomized arms. Three patients in the 100 mg QD arm discontinued dasatinib vs 9 patients in all the other arms (19, 20).

On the whole current recommendations for management of pleural effusions related to dasatinib administration consist in the correct information at start of therapy about possible risk of pleural effusions and patient's education to early recognize and report relevant symptoms (chest pain, dyspnoea and dry cough) (35). When pleural effusion is diagnosed by chest-Xray or CT scan, it is suggested to discontinue dasatinib. In case of patient without symptoms or returning after discontinuation to normal conditions, it is suggested to restart (after X-ray showing complete resolution) with the same drug dose after first episode, and to reduce the dose to 80 mg/day after second episode to maintain the maximum possible dose related to best efficacy. In case of grade 3/4 event, even if it

is the first, it is recommended to restart at resolution with low dose of dasatinib but this has to depends on individual clinical circumstances. If, after discontinuation, no improvements are evidenced it is suggested to exclude effusions related to other conditions (second malignancies, infections) and in the absence to start with steroids (prednisone 25 mg/day, for the possible immunosuppressive action on the increased lymphocyte population) and diuretics (furosemide 25 mg two times a day) (35,36) (figure 1). In patients with recurrent pleural effusions it is also conceivable to switch to another TKIs, due to the absence of cross intolerance reported with other drugs (8,9).

Conclusion

Pleural effusion is a quite frequent complication of dasatinib therapy in CML: it is usually reported as manageable, mild to moderate in severity, occurring more frequently in advanced phases of disease, in elderly patients with concomitant comorbidities and in patients treated with high drug dosage. What type of comorbidities are the main frequent associated to pleural effusions remained to be elucidated. Several authors reported that pre-existing cardiovascular diseases predisposing to the onset of this quite common adverse event with dasatinib, both in patients treated after

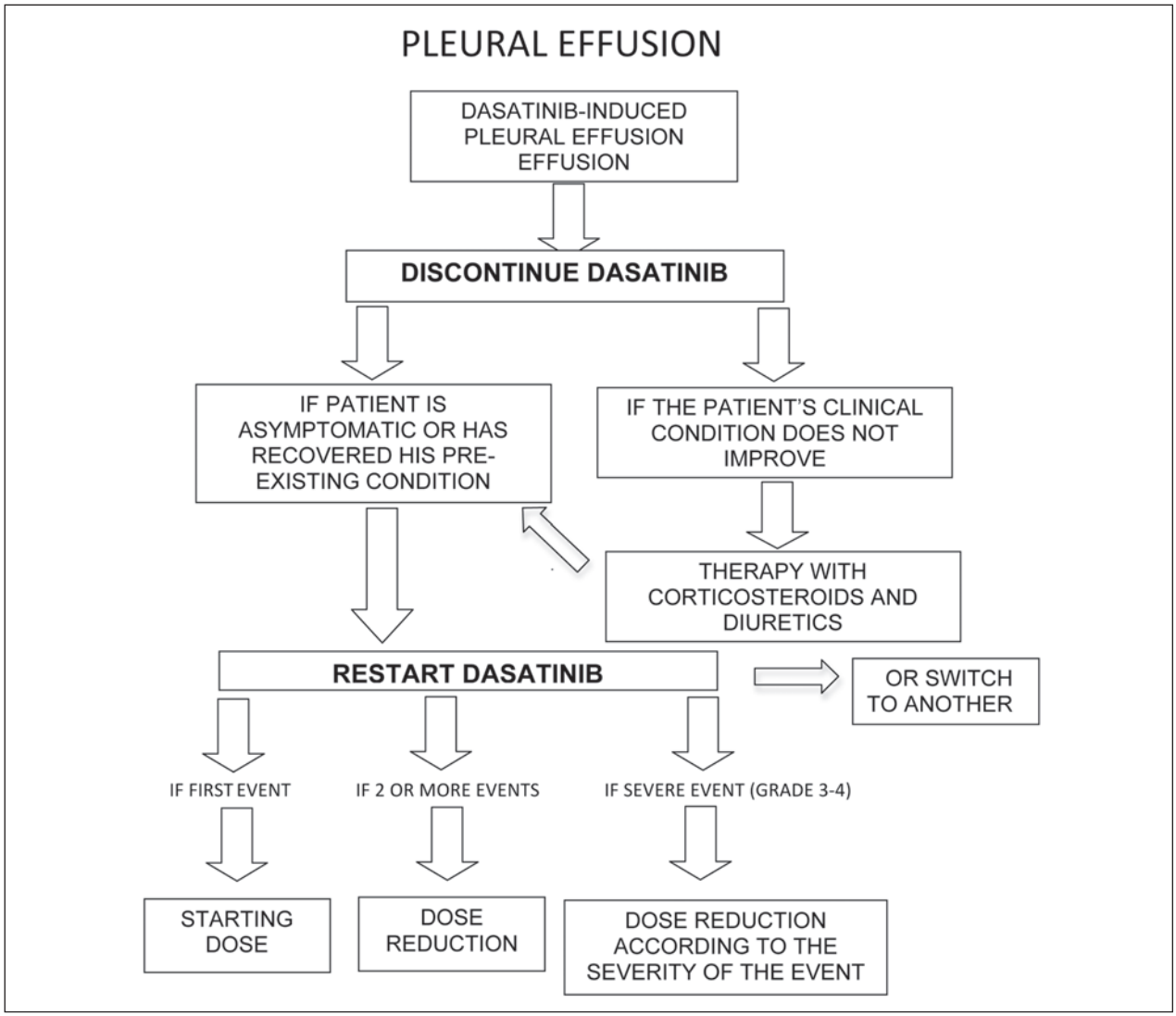

Figure 1. Algorithm for the managment of adverse events

imatinib failure or frontline. In particular, in a subanalysis of DASISION trial (36), it has been reported that pleural effusions were more frequently observed in patients affected by hypertension. Concomitant presence at baseline of previous cardiovascular events, or other major risks such as hypertension, obesity, dyslipidemia, predispose patients to increased risk of effusions: it remain unclear the role of severe renal impairment and diabetes that should be prospectively assessed as potential risk factors. The application of a comorbidity score index may be of help to indicate patients at higher risk of pleural effusion development: these patients need a close monitoring of adverse events during dasatinib treatment.

Multi-factorial pathogenesis has been proposed: tyrosine-kinase inhibition or immune-mediated effects involving other tyrosine kinases (TEC or BTK of lymphocyte B and T signalling) are the main mechanisms suggested. The management of this side effect includes temporary dasatinib discontinuation, dose reduction, use of steroids and diuretics and, only in a few severe instances (grade 3/4), therapeutic thoracentesis. Clinical practice has shown that these side effects are generally reversible following transient treatment suspension. Only retrospective data showed that intermittent therapy with dasatinib could reduce the grade of pleural effusions and other toxicities, without compromising efficacy, but this was never confirmed in a prospective trial (30).

Long-term follow-up of sponsored clinical trials showed that pleural effusions occurred in 25-27% of patients after 5-7 years of treatment. Correct information regarding type of symptoms associated to the onset of pleural effusions at start of therapy should be provided in order to reduce the number of high-grade effusions. Pleural effusions could also be associated to a rare but possible side effect of dasatinib, pulmonary arterial hypertension (PAH). By 3-year follow-up of DASISION trial (37), pulmonary hypertension was reported in 8 patients receiving dasatinib, but right heart catheterization, required to confirm PAH was performed only in 1 patient. PAH is a rare group of clinical severe conditions characterized by pre-capillary increased pressure: it has been reported a female predominance, a longer median time of occurrence between start of drug and onset of disease always associated to severe signs of hemodynamic heart failure. Withdrawal of dasatinib in most of the cases has been reported associated to improvement of PAH and complete resolution. PAH represents, together with recurrent pleural effusions, although the use of low dasatinib dose, the situations that required discontinuation of the drug. Due to possible association with effusions, PAH should be excluded every time patients in treatment developed dyspnea (38). To reduce the risk of PAH, patients should be evaluated for signs of underlying cardiopulmonary disease before starting with dasatinib (Figure 2). Hence, future researches should

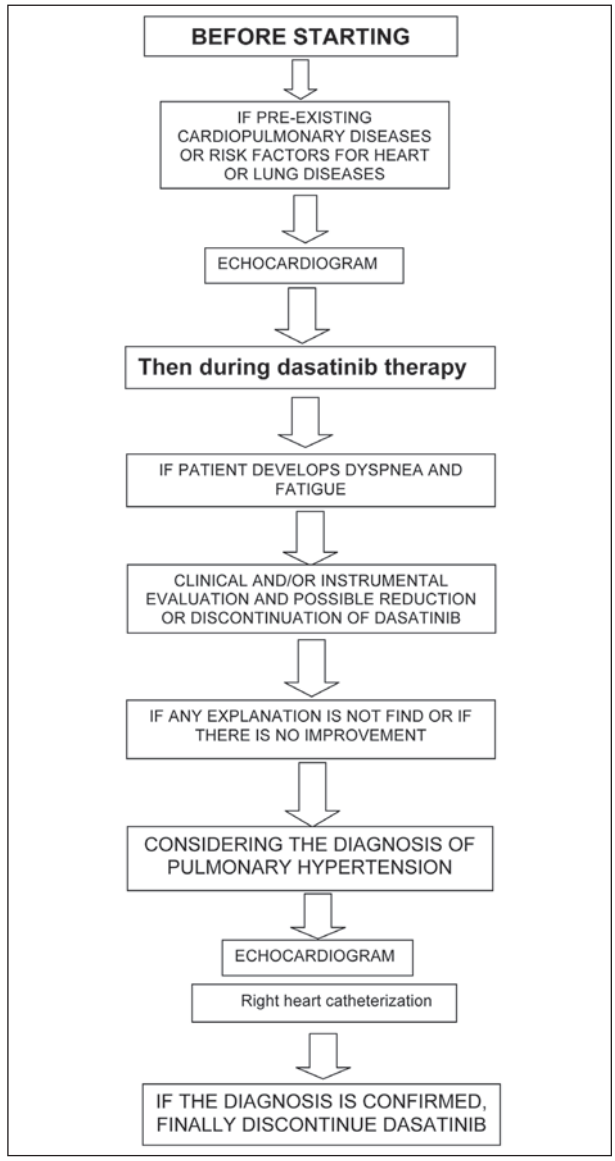

Figure 2. Algorithm for the management of adverse events

be focus on prospective cardiologic monitoring with echocardiogram to identify patients with increased risk of PAH and to estimate an approximate incidence of patients who should be candidate to right heart catheterization. Future efforts should be focused also to identify possible target(s) of the drug responsible of effusions and to understand how to prevent its inhibition. Future studies are warranted also to clearly explain similarity between effusions and PAH and to clearly understand if patients who developed effusions are also at risk of this important side effect. Moreover, in this order a correct stratification of patients at the time of start of the drug with evaluation of cardiac and pulmonary conditions at baseline could reduce the risk of this side effect in the long term.

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Address: Massimo Breccia, MD
Department of Cellular Biotechnologies and Hematology
Sapienza University
Via Benevento 6, 00161 Rome, Italy
Tel. 003906857951
Fax 00390644241984
E-mail: breccia@bce.uniroma1.it