The incidence of pleural and pericardial effusion is not higher in patients receiving dasatinib at low doses. (Reply)

In a recent issue of this Journal, Krauth *et al.*[1] reported the development of extensive pleural or pericardial effusions in 4 chronic myeloid leukemia (CML) patients treated for at least three months with average or low dose (100 or 50 milligrams/day) dasatinib. The Authors consecutively treated 13 patients with dasatinib at 50 or 100 mg daily for at least three months (range 3-38), and observed extensive pleural or pericardial effusion in approximately 30% of the patients. They conclude that CML patients treated with dasatinib are at risk of developing pleural or pericardial effusion, even when the drug is administered at average (100 mg/day) or low (50 mg/day) doses, and independently from pre-existing pulmonary or cardiac disease.

In our opinion, this information is misleading for several reasons. First, 2 of 4 patients developing a grade III/IV pleural effusion were in accelerated phase. Several studies demonstrated that advanced disease CML, either in accelerated or blastic phase, is significantly associated with a higher risk of pleural effusion, independently of dasatinib dose, together with history of cardiac disease, hypertension and b.i.d schedule.[2,3] Second, one out of 4 patients received an allogeneic stem cell transplantation and suffered chronic graft-*versus*-host disease of the skin. The Hammersmith group[3] has reported that a previous history of autoimmune disorders or a history of skin rash during imatinib therapy are variables associated with higher risk of developing a pleural or pericardial effusion. Even if Krauth and co-workers did not describe the development of skin rash during imatinib, it is possible to hypothesize a history of autoimmune disease due to chronic graft-*versus*-host disease of the skin. As a matter of fact, 3 out of 4 patients reported in this paper had one or more risk factors for developing pleural or pericardial effusion already present at the time of starting dasatinib.

Table 1. Patients' characteristics (n=114).

Characteristics	Number
Age, years	
Median	56.5
Range	21-82
Pts aged >60 years	50 (40%)
Pts aged >70 years	19 (15%)
Sokal risk group	
Low	29
Intermediate	45
High	40
Disease characteristics	
Imatinib resistant	88
Intolerant to imatinib	16
Resistant and intolerant	10
Time in dasatinib, months	
Median	19
Range	6-43
Pleural effusion (all 114 patients)	4 (3%)
Pericardial effusion (all 114 patients)	1 (0.8%)

This information should be kept carefully in mind when we read this paper, because the population of patients treated was at high risk of developing fluid retention.

Third, the conclusions expressed by Krauth *et al.*[1] are in contrast with results published on larger series of CML patients treated with up to 100 mg/day. Porkka *et al.*[4] presented the data on the incidence of pleural effusion in the phase III trial for chronic phase patients comparing four different dosages of dasatinib (Study 034). The occurrence of effusion of all grades was 14% in the 100 mg q.d arm compared to 25% in the 70 mg b.i.d arm (P=0.021), with a slight increase in the overall rate between the first and second year of follow up. We recently published the results from a real life-based Italian multicenter study on 114 CML patients in chronic phase treated with dasatinib due to resistance or intolerance to imatinib.[5] Patients' characteristics are summarized in Table 1. Patients received dasatinib at different doses, starting from at least 100 milligrams/day. As a matter of fact, patients experiencing a grade III-IV toxicity discontinued dasatinib or, if possible, reduced the dose from 140 or 100 milligrams/day to 70 or 50 milligrams/day. When patients maintained or improved their response even with low doses of dasatinib, we decided to proceed with the tolerated dose of the drug. At the time of the analysis, 56 patients were receiving 50 or 70 milligrams/day of dasatinib, whereas 58 patients were receiving 100 or 140 milligrams/day. Patients were treated with dasatinib for a median time of 19 months (range 6-39).

Only 4 of 114 patients (3%) and one of 114 (0.8%) suffered from a grade III-IV pleural or pericardial effusion. Remarkably, none of the 56 subjects receiving low doses of dasatinib (50 or 70 mg/day) experienced a grade III-IV pleural effusion.

Pleural, as well as pericardial effusions are potentially serious and must be treated promptly.[6] However, pleural effusions are usually manageable, generally mild to moderate in severity, and occur more frequently in advanced phase of disease, in elderly patients with concomitant comorbidities and in patients treated with high doses. In conclusion, we agree that the possible occurrence of fluid retention should not be underestimated while treating CML patients with dasatinib, in particular if they present comorbidities. On the other hand, our data,[5] drawn from a real-life approach, are reassuring not only regarding efficacy, but even regarding tolerability and feasibility of dasatinib treatment at low doses. A word of caution should be expressed on the possible overestimation of the incidence of effusion, a fact that could prevent physicians administering a drug such as dasatinib, which is effective and generally safe for CML patients, especially at average or low doses.

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