On the safety of low-dose dasatinib in comorbid and non-comorbid patients: what is real-life? (Reply)

We are writing in response to the Letter of Dr. Guiseppe Visani and colleagues, 'The incidence of pleural and pericardial effusion is not higher in patients receiving dasatinib at low doses'.[1] We agree that in our study, non-comorbid and comorbid patients and those with accelerated phase disease were included.[2] We also agree that in patients with Ph+ chronic myeloid leukemia (CML) treated with low-dose dasatinib (50-100 mg/day), the incidence of pleural and pericardial effusions is lower (definitively not higher) compared to high-dose dasatinib (140 mg/day).[3] This was also found in our patients.[2,4] In addition, we agree that in 'chronic phase-patients' without comorbidity the frequency of effusion formation may be lower.[5] Finally, first-line dasatinib at low dose[6] may even be less toxic compared to second-line dasatinib used in pre-treated patients.[3,5]

However, unfortunately, the 'real-life' to which the authors refer in their letter usually includes both patients without *and* patients with comorbidities, and in the second-line setting, to which most published data and our data refer, many patients have suboptimal response or even show signs of disease-acceleration[2-5] (then 140 mg dasatinib/day is often recommended). In addition, such patients tend to develop comorbidities such as infections and weight-loss during dasatinib.[4] Therefore, we do not agree with the authors' conclusion that our information is misleading, but would rather argue that their statement[1] is questionable, as it would suggest that real life exists without comorbidities, drug resistance, or disease-acceleration.

Where we agree is the fact that the frequency of pleural effusions in second-line patients treated with low-dose dasatinib is lower compared to second-line patients treated with high-dose dasatinib (140 mg/day). Notably, in our (small) patients' cohorts, including both comorbid and non-comorbid patients, the difference in the frequency of pleural effusions is clearly visible:[2,4] in fact, whereas 75% of patients at 140 mg daily developed pleural effusions (grade II or higher) over time,[4] only 56% of those who started at 50 or 100 mg/day developed pleural effusions.[2] Why these frequencies are still higher when compared to the available literature may have several explanations. One may be the fact that this side effect is accumulating over time. Another explanation may be under-reporting in clinical trials.[7] Notably, in most studies, chest X-rays were only performed routinely until 'month 6', and later only if symptoms were noted,[3,6] whereas in our center, all dasatinib-treated patients had repeated chest X-rays over the entire time period (at least once a year). In other words, most other published data refer only to the frequency of *symptomatic* pleural effusions. There may also be other reasons for under-reporting which we have discussed recently.[7]

Finally, we would like to state that we believe that a repeated chest X-ray should indeed be considered in both younger (non-comorbid) and older (often comorbid) patients: in older patients because of the comorbidity-associated risk, and in younger patients because they are potential candidates for stem cell transplantation. For such patients it may be a less favorable scenario if effusion-formation or viral infection/reactivation is overlooked before they are referred.

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