Is there something wrong in paradise? Christian beliefs and the safety of novel BCR/ABL1 inhibitors

We take the liberty and opportunity to discuss adverse events and event reporting in patients with chronic myeloid leukemia (CML) treated with second generation BCR/ABL1-targeting drugs. The study of Ahmet Emre Eskazan[1] suggests that CML patients treated with low-dose dasatinib (100 mg daily) may develop pleural effusions at a higher frequency than that reported in published clinical trials.[2,3] Thereby, these data confirm our own observations.[4,5] Many other centers where chest X-rays are now performed in dasatinib-treated *asymptomatic* patients on a routine basis because of the apparent risk, and to detect pleural effusion earlier, may have the same experience. In fact, although not stated explicitly in all studies, the frequency reported in these published trials was the frequency of *symptomatic*, but not total/all, pleural effusions, because most studies with dasatinib did not include a long-term follow up of routine chest X-rays, which is a remarkable neglect (original text in first line trial: after six months done only if indicated clinically[3]). In addition, most centers may have noticed that during treatment with dasatinib, viral reactivation and opportunistic (atypical) infections may occur[4], although in most trials, such adverse events were not reported.

There is a similar emerging problem with nilotinib. In fact, the recently described "metabolic effect" of nilotinib with elevations in fasting glucose levels that is sometimes measurable[6] (and Aichberger *et al.*, submitted manuscript, 2011) and the occurrence of progressive arterial occlusive disease in several of these patients (Aichberger *et al.*, submitted manuscript, 2011) have been recognized as possibly related and recurrent adverse event in various centers including our center; although again, such vascular events were not reported in published clinical trials so far.[7,8] Remarkably, no such adverse event accumulation (vascular events) was noted in the very same patients during their prior treatment with imatinib, i.e. prior to their switch to nilotinib (Aichberger *et al.*, submitted manuscript, 2011).

Before discussing potential reasons underlying the selective accumulation of such adverse events in our center (pleural effusions during dasatinib 100 mg/day: 56%;[5] vascular events during nilotinib, 800 mg/day: 25% (Aichberger *et al.*, submitted manuscript, 2011) and a few other academic centers, I would like to draw the reader´s attention to some drug features that one can extract from recently published studies.[2,3,7,8] Notably, compared to the expected frequency of common vascular disorders in the normal population and infectious events in CML patients, dasatinib at 100 mg daily as *per* published data must protect CML patients completely from any type of viral or bacterial infectious disease,[3] and nilotinib 300 and 400 mg twice daily, apparently protects from any type of vascular occlusive or severe coronary artery event.[7,8] In other words, whereas in our center the frequency of such adverse events during dasatinib or nilotinib, respectively, is about 10-100 times higher when compared to the normal or CML population, it was not reported during first-line dasatinib or nilotinib in recently published trials. These examples already provide a clue and potential explanation, which is in our opinion under-reporting of events. Therefore, the real question may be: what are the reasons for under-reporting? Since no in depth re-analysis of published data is available, my letter will not be able to provide a definitive answer to this question, but will try to address some potential issues. Lastly we also cannot exclude that our center was just unlucky with all these events on 3 consecutive occasions: dasatinib 140 mg daily,[4] dasatinib 100 mg daily,[5] and nilotinib 800 mg daily (Aichberger *et al.*, submitted manuscript, 2011).

In general, under-reporting could be on purpose (e.g. triggered by interests) or alternatively, may happen because the event or event-drug-relationship had just been overlooked. Our belief is in the latter. There are many reasons to explain why events had been overlooked. One is lack of experience or the need to keep costs within a certain limit (e.g. repeated chest X-rays in asymptomatic patients or repeated virus serology: this may count in daily practice). Another reason may be the rather frequent occurrence of certain events in the normal population, like peripheral arterial occlusive disease or diabetes mellitus (even viral infections), so that one would not think of a relationship unless events are very unusual or accumulate with unusually high frequency. An alternative explanation may be that pre-therapy with imatinib or other anti-CML drugs increased the risk, which would explain the difference in the frequencies of events reported in first-line trials and observations made by us and by others in second-line patients[1,4,5] (and Aichberger *et al.*, submitted manuscript, 2011). An unrelated additional reason is the difficulty to publish such "novel results" against what has been believed to be absolutely invariable robust data from larger case series. In addition, adverse events may accumulate over time (also pleural effusions) or may be related to a certain dose of BCR/ABL1 inhibitors. With regard to dasatinib-induced pleural effusions, we can now state that lowering the dose of dasatinib does at least not eliminate the risk for development of clinically relevant effusions, as confirmed by Ahmet Emre Eskazan *et al.*[1] The reason for this phenomenon (low-dose dasatinib-induced effusion) remains unknown. One explanation would be that low-dose dasatinib is still capable of promoting the activation of certain immune cells that release vasoactive mediators in tissues. In this regard, it is important to state that the short half-life of dasatinib is clearly in favor of low or even very low drug concentrations in tissues. This hypothesis would also be supported by the observation that very low concentrations of dasatinib promote *in vitro* histamine release from activated human blood basophils.[9]

Based on the unclear (but maybe higher than believed) frequency of certain relevant adverse events, our recommendation is to frankly assist and truly support us in the evaluation of side effects provoked by BCR/ABL1 blockers, and in studying related mechanisms and strategies of prevention and event management, since proper patient-selection or/and co-medication may be sufficient to keep such events to an minimum or at least at acceptable low frequency. This is of importance as some of these adverse events are severe or even life-threatening and can easily lead to non-transplantable condition. It is also important to start here now timely, because both BCR/ABL1 blockers have already received approval for first line treatment of freshly diagnosed CML.

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