Pulmonary complications of tyrosine kinase inhibitors in myeloproliferative disorders

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The pulmonary physician must be aware of pulmonary toxicities if patients are treated with tyrosine kinase inhibitors. The compounds have different therapeutic targets and are associated to different extents with pulmonary complications. https://bit.ly/3gXUF8h


Life has changed for patients with chronic myeloid leukaemia (CML) since the introduction of breakpoint cluster region–Abelson (Bcr-Abl) tyrosine kinase inhibitors (TKIs) in the late 1990s. Before the era of the TKIs began, the 5-year overall survival rates for patients with CML were approximately 28–66%, depending on risk group, chemotherapy regimen and interferon use [1]. In 1996, the first oral TKI was investigated in pre-clinical studies and showed an astonishing reduction of tumour cell formation [2]. This TKI, later named imatinib, was the first to gain US and EU approval for CML in 2001 [3–5] and dramatically increased long-term survival rates to 76–94% at 6 years, depending on risk group [6]. Since then, various generations of Bcr-Abl TKIs have been developed, which induce even higher and faster rates of complete cytogenetic response than first-generation TKIs. To date, Bcr-Abl TKIs provide the basis for successful treatment of the underlying myeloproliferative disease [7].

However, this treatment class is not without toxicity. In the early years of development, the side-effect profile of the first-generation TKIs was considered rather benign, with vomiting, diarrhoea, anaemia and neutropenia observed at the highest dose levels in pre-clinical studies of imatinib [8] and minimal adverse events (most commonly nausea, myalgias, oedema and diarrhoea) reported in a pivotal clinical trial [3]. However, from 2007 onwards it became evident from case reports and retrospective registry analysis that Bcr-Abl TKIs exhibit cardiac [9] and predominately clinically relevant pulmonary toxicities [10–12], independent of the pulmonary complications associated with leukaemia per se [13].

In the present issue of the European Respiratory Journal, Weatherald et al. [14] comprehensively review the pulmonary complications of TKIs. They summarise key pathophysiological mechanisms and conclude that endothelial dysfunction, direct cell toxicity, enhanced cellular levels of reactive oxygen species, and/or inflammatory events contribute to the occurrence of pulmonary complications [14, 15]. Interestingly, besides sharing the major target of the Bcr-Abl oncogene, members of the presented TKI family have substantial differences in other molecular targets and occurrence of pulmonary complications.
particular, a relevant number of studies only reported events occurring in lung fibrosis of any severity were pooled. Risk ratios and 95% confidence intervals were calculated using the Mantel Haenszel method with continuity correction in R version 4.0.0 (The R Foundation, Vienna, Austria). Limitations: we did not have access to source data from the trials. In particular, a relevant number of studies only reported events occurring in \( \geq 10\% \) of patients.

This diversity of the Bcr-Abl TKI family has implications not only for the treatment of myeloproliferative disorders but also for investigations in other indications.

In 2005 (a little while before awareness of pulmonary complications began to grow), emerging pre-clinical and case report data suggested that the very first TKI imatinib might even have beneficial effects on the pulmonary vasculature [16, 17]. The pre-clinical findings in particular were considered very promising at the time: imatinib was the first agent of this class to show the ability to reverse experimentally induced pulmonary hypertension (PH) by exerting anti-proliferative and pro-apoptotic effects in the pulmonary vasculature [17]. In a clinical trial including patients with pulmonary arterial hypertension (PAH), imatinib improved haemodynamics and exercise capacity [18, 19]. However, the study design and outcome interpretation of the results were the subject of ongoing debate. Approval of imatinib for PAH was not sought, owing to the occurrence of serious non-pulmonary adverse events (including subdural haematoma in patients receiving anticoagulation [18, 19]).

Nevertheless, as highlighted by the review of Weatherald et al. [14], imatinib and newer members of the TKI family such as nilotinib, bosutinib, ponatinib and, especially, dasatinib were found to be associated with a high incidence of pulmonary complications, such as pleural effusion and even induced PH or interstitial lung disease (lung fibrosis) of any severity were pooled. Risk ratios and 95% confidence intervals were calculated using the Mantel–Haenszel method with continuity correction in R version 4.0.0 (The R Foundation, Vienna, Austria). Limitations: we did not have access to source data from the trials. In particular, a relevant number of studies only reported events occurring in \( \geq 10\% \) of patients.

Nevertheless, as highlighted by the review of Weatherald et al. [14], imatinib and newer members of the TKI family such as nilotinib, bosutinib, ponatinib and, especially, dasatinib were found to be associated with a high incidence of pulmonary complications, such as pleural effusion and even induced PH or interstitial lung disease in individual cases. This prompts the question: do all Bcr-Abl TKIs lead to similar pulmonary complications or might imatinib show a more favourable profile? To address this question, we performed a systematic meta-analysis of the new-generation Bcr-Abl TKIs (included in the review by Weatherald et al. [14]) versus imatinib. We included data from eight randomised, controlled, phase 3 clinical trials (seven in patients with CML, and one in patients with metastatic gastrointestinal stromal tumours) with imatinib as the control [20–27]. Our data showed that the risk ratio of all-grade pulmonary complications with new-generation TKIs compared with imatinib was 3.56 (95% CI 0.78–16.29) overall, albeit with a significant degree of heterogeneity (\( I^2=80\% \)). The risk ratio varied depending on the new-generation TKI, and was highest for dasatinib (figure 1).
That being said, the beneficial effects of imatinib on pulmonary haemodynamics in patients with PAH [18] may still merit further investigation. A more careful selection of patients, excluding for instance patients receiving anticoagulation and introducing mandatory imaging of the brain before therapy, might even pave the way for imatinib to become indicated in PAH. As disease-modifying drugs in PH are rare, trials using anti-proliferative drugs are urgently needed. With knowledge of the adverse event profile and careful monitoring, studies using repurposed imatinib (www.clinicaltrials.gov NCT04416750) or inhaled modifications [28] in PH are feasible.

We congratulate Weatherald et al. [14] for their comprehensive review and for bringing the pulmonary complications of Bcr-Abl TKIs to the front desk of the European Respiratory Journal. The pulmonary physician has to be aware of pulmonary toxicities if patients are treated with Bcr-Abl TKIs, because despite being a united TKI family, the compounds have different therapeutic targets and are associated to different extents with pulmonary complications.

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