Identification of cellular targets involved in cardiac failure caused by PKI in oncology: an approach combining pharmacovigilance and pharmacodynamics.

Patras de Campaigno E, Bondon-Guitton E, Conte Cécile, Laurent G, Montastruc F, Montastruc JL, Lapeyre-Mestre M, Despas F.

1. (Service de Pharmacologie Médicale et Clinique, CHU de Toulouse, 37 allées Jules Guesde, 31000, Toulouse, France.
2. UMR1027, Inserm, Université Paul Sabatier, Toulouse, France.
3. Service de Pharmacologie Médicale et Clinique, Faculté de Médecine, Université Paul Sabatier, Toulouse, France.
4. Centre Midi-Pyrénées de Pharmacovigilance, de Pharmacocypidémiologie et d'Informations sur le Médicament, Centre Hospitalier Universitaire de Toulouse, Toulouse, France.
5. Département d'Hématologie et de médecine Interne, Institut Universitaire du Cancer Oncopole, 1 Avenue Irène Joliot-Curie, Toulouse, France.
6. INSERM CIC 1436 Toulouse, Centre d'Investigation Clinique de Toulouse, Centre Hospitalier Universitaire de Toulouse, France.

Purpose:
The aims of the present study were to evaluate the risk of cardiac failure (CF) associated with 15 anticancer protein kinase inhibitors (PKIs) through a case/noncase analysis and to identify which PK(s) and pathways are involved in PKI-induced CF.

Experimental Design:
In order to evaluate the risk of CF, adjusted reporting odds ratios (aRORs) were calculated for the 15 anticancer PKIs in the World Health Organization safety report database (VigiBase®). We realised a literature review to identify 21 protein kinases (PKs) that were possibly involved in CF caused by PKIs. Pearson correlation coefficients (r) between aRORs and affinity data of the 15 PKIs for the 21 PKs were calculated to identify the cellular target most likely to be involved in PKI-induced CF.

Results:
A total of 141 601 individual case safety reports (ICSRs) were extracted from VigiBase® for the following PKIs: afatinib, axitinib, bosutinib, crizotinib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, ruxolitinib, sorafenib, sunitinib and vandetanib. Among them, 2594 ICSRs concerned CF. The disproportionality analysis revealed that, for dasatinib, imatinib, bosutinib, sunitinib and nilotinib, disproportionality for CF was significantly higher than for other PKIs, with aRORs of 2.52 [95% CI 2.26, 2.82], 1.79 (95% CI 1.57, 2.03), 1.73 (95% CI 1.18, 2.54), 1.67 (95% CI 1.51, 1.84) and 1.38 (95% CI 1.18, 1.61), respectively. Significant values for correlation coefficients between the product of dissociation constant (pKd) and aOR were observed for two non-receptor protein kinases: ABL1 (non-phosphorylated and phosphorylated forms) and ABL2 protein kinases, with values of r = 0.83 (P = 0.0001), r = 0.75 (P = 0.0014) and r = 0.78 (P = 0.0006), respectively.

Conclusion:
We observed a higher disproportionality for CF with dasatinib, imatinib, bosutinib, sunitinib and nilotinib than with other PKIs. In addition, the study highlighted the role of ABL tyrosine kinases in CF caused by anticancer PKIs.