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EDITORIAL

Imatinib: the controversial discussion on cardiotoxicity induced by endoplasmic reticulum (ER) stress

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The safety profile of imatinib, and especially its relevance to cardiotoxicity, has been controversially discussed in recent years (Kerkelä et al. 2006; Herman et al. 2011; Wolf et al. 2010; Ribeiro et al. 2008). Therefore, the editors are pleased that Eirini Thanopoulou and Ian Judson from the Royal Marsden NHS foundation Trust in London contributed a comprehensive review on the long-term tolerability of imatinib (Gleevec) (Thanopoulou and Judson 2012).

The introduction of imatinib represents one of the most prominent success stories in cancer therapy of the past decade. A reciprocal translocation creating the Philadelphia chromosome is involved in pathogenesis of more than 90% of the cases of chronic myelogenous leukaemia (CML) (Van Etten 2004). This translocation creates the Bcr-Abl fusion protein of the nonreceptor tyrosine kinase c-Abl and the multidomain protein Bcr, leading to a constitutively active cytosolic protein that activates several signalling pathways involved in proliferation and anti-apoptosis. Imatinib inhibits the fusion protein, Bcr-Abl resulting in remission in a high fraction of patients with CML. In addition, imatinib is efficient in gastrointestinal stromal tumour (GIST), because—besides its effect on Bcr-Abl—it also inhibits KIT proteins that play a role in progression of GIST and other tumours (Joensuu et al. 2001; Micke et al. 2003, 2004). The success stories of imatinib, and the Her-2-targeting antibody, trastuzumab, led to the novel concept of identifying and targeting the mechanisms responsible of tumour progression, in addition to identifying subtypes of carcinomas with the perspective of a biologically justified therapy (Schmidt et al. 2008, 2010; Hellwig et al. 2010; Cadenas et al. 2010; Lee et al. 2010; Brase et al. 2010; Petry et al. 2010).

Previously, Kerkelä et al. (2006) reported on the cardiotoxic side effect of imatinib. Individuals without any prior history of heart disease developed heart failure after treatment with imatinib (Kerkelä et al. 2006). Interestingly, imatinib also showed toxic effects on cultivated cardiomyocytes, most likely due to an induction of endoplasmic reticulum (ER) stress, leading to decreased translation and a block in protein synthesis (Kerkelä et al. 2006). A simultaneous upregulation of stress response genes suggested that the ER stress response is an adequate mechanism to compensate short-term cell stress. However, prolonged activation may induce cell death by pathways, including Jun N-terminal kinases (JNKs), a mechanism shown for imatinib in cardiomyocytes (Kerkelä et al. 2006). Since cardiotoxicity is one of the leading topics in toxicology addressed in our journal (Sumi et al. 2011; Vávrová et al. 2011; Lee et al. 2010), we welcome the current review by Thanopoulou and Judson (2012). Overall, imatinib shows an excellent long-term tolerability and the clinical relevance of imatinib-induced cardiotoxicity may have been overestimated. The comprehensive review of Thanopoulou and Judson (2012) comes highly recommended for anyone interested in the safety profile of imatinib.

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