Arrhythmia: an ‘off-target’ effect of cancer cardiotoxicity

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Spontaneous Ca^{2+} release *via* cardiac ryanodine receptors (RyR2) can occur under conditions of SR Ca^{2+} overload, a process termed store-overload–induced Ca^{2+} release (SOICR), and is known trigger for arrhythmia. ATP based kinase inhibitors are an increasing class of drugs used to treat cancer. Several of these compounds have been linked to arrhythmias in clinical trials, but the underlying mechanism is unknown. ATP is an agonist for RyR2, therefore we hypothesized that the arrhythmogenic nature of ATP based kinase inhibitors is due to an “ATP-like” activation of RyR2 leading to SOICR. To explore our hypothesis we examined four ATP based kinase inhibitors; CX-4945, sunitinib, ponatinib and nilotinib. CX-4945 and sunitinib are competitive ATP inhibitors (class I) and could be expected to bind to the ATP site within RyR2, whereas ponatinib and nilotinib are allosteric ATP inhibitors (class II). We found that both CX-4945 and sunitinib significantly increased the propensity for SOICR, whereas neither class II resulted in any changed compared to vehicle control. We confirmed a direct effect of the class I inhibitor CX-4945 on RyR2 using single channel recordings. The application of CX-4945 did not increase channel open probability but did induce regular prolonged openings consistent with the observed increase in SOICR.

Combined these data suggest that class I ATP based kinase inhibitors may be pro-arrhythmogenic due to the ability of these drugs to interact with the ATP binding site and trigger SOICR.