International Journal of Cardiology 176 (2014) 1082–1085

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Letter to the Editor

HERG-targeted therapy in both cancer and cardiovascular system with cardiovascular drugs

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ARTICLE INFO

Article history:
Received 27 May 2014
Accepted 26 July 2014
Available online 2 August 2014

Keywords:
Cancer chemotherapy
Cardio-oncology
Cardiotoxicity
HERG
Multidrug resistance (MDR)
Torsade de pointes arrhythmia(TdP)

The progress in the cancer knowledge and treatment has led to a new frontier: the cardio-oncology [1–36]. Nowadays cardiotoxicity prevention still remains an important challenge as well as its surveillance and management in cancer survivors [31–36] but research suggests that cardiologists can play an active role beyond the heart defense in cancer therapy. Before oncology walked on the human ether-a-go-go-related gene [HERG] K^+ channel-targeted therapy roads [37–40], HERG-targeted drugs has been proven useful and safe not only for common cardiological use but also as anticancer therapy. HERG (hERG; Kv11.1, KCNH2) encodes the rapid delayed-rectifier K^+-current (I_{Kr}) [41] having an essential role in cardiac action potential repolarization [38]. HERG blockade can lead to QT prolongation [42–55] with increased risk of potentially life-threatening torsade de pointes arrhythmia (TdP) [56–63]. Several HERG-blockers have been withdrawn from post-approval surveillance [62-64]. Additionally research has suggested that HERG is over-expressed in a wide range of human cancers controlling cell proliferation, migration and death [38,42,47,52,65,66]. Effectiveness of several cardiovascular drugs in cancer controlling has been suggested in the past [67] but the development of the research has highlighted the importance of their HERG-blockade properties. Ranolazine is illustrative of the translational success of the cardio-oncological pharmacology [68-77]. Ranolazine [68–72], an anti-ischemic agent, in addition to late INa (INaL) inhibits I_{Kr} [encoded by HERG] [73–75] and causes a time- and voltage-dependent, but frequency-independent, block of HERG. The kinetics of HERG inhibition (at positive potentials) and unblock (upon hyperpolarization) by ranolazine are rapid. These distinct and rapid kinetic interactions of ranolazine with HERG may partially contribute to the observations that the drug is not proarrhythmic despite causing a small prolongation of action potentials and QT intervals [62,76]. Nevertheless this evidence, a case of TdP has been described [77]. Research has reported both the cardioprotective use of ranolazine against cardiotoxic chemotherapies and the use of ranolazine as an anti-metastatic agent [78]. The small molecule HERG ligand quinazoline-derived [79] alpha1-adrenoceptor antagonist anti-hypertensive doxazosin [38] is capable of inhibiting malignant behaviors in vitro and in vivo and it is also the agonist of a receptor tyrosine kinase triggering ephrin type-A receptor 2 [EphA2] internalization that suppresses haptotactic and chemotactic migration of prostate cancer, breast cancer, and glioma cells [80,81]. The 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor, rosuvastatin [81–93], is an HERG and I_{Kr} blocker with anticancer effect [81,94]. Disruption of intracellular cholesterol homeostasis with simvastatin impairs HERG channel trafficking [95]. Low-potency blocker lovastatin blocks HERG in a concentration-dependent manner without signs of use dependence and with cardiac safety recorded clinically [96](only a case of QTc prolongation due to interaction between quetiapine and lovastatin has been reported) [97]. Research suggests lovastatin anticancer effect [98,99]. Propafenone and its main active metabolite, 5-hydroxypropafenone, block HERG channels [100–102] by binding predominantly to the open state of the channel [103]. Propafenone's blockade of HERG was strongly dependent on residue Phe656 [103]. In addition propafenone-type P-gp inhibitors act against the overexpression of xenotoxin transporter P-glycoprotein (P-gp) that represents one major reason for the development of multidrug resistance (MDR), leading to the failure of antibiotic and cancer therapies [104] and exerts anticancer activity [105]. Only four reports of TdP have been reported in the literature during propafenone treatment(associated with ibutilide [106],after quinidine therapy [107] in a hypothyroid patient with ventricular preexcitation [108] and in another case associated with lidocaine during acute myocardial infarction [109]) but propafenone is not considered to cause TdP [62]. Verapamil causes a high-affinity block of HERG current [110] but is free from QT prolongation in human; this is probably explained by its multiple interactions with cardiac ion channels [111] also inhibiting TdP [62, 112]. Moreover verapamil exerts anticancer properties [113–117], is also significantly reducing epidermal growth factor receptor (EGFR)

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http://dx.doi.org/10.1016/j.ijcard.2014.07.129

expression [118] and is a specific inhibitor for plasma membrane drug transporter P-glycoprotein (Pgp) encoded by the multidrug resistance protein 1 (MDR1) (ABCB1) gene [116,119] improving chemotherapy response in cancer [118,119]. Diltiazem weakly [110,120–122] blocks HERG current and is effective in protecting against doxorubicin-induced cell toxicity. Carvedilol, propranolol and metoprolol are inhibitors of HERG current in a concentration-dependent manner and not frequency-dependent [123]. Sotalol has a risk of causing TdP [40]. A possible beneficial effect of β-blockers against the risk of cancer development [124] and a prolonged survival of cancer patients [125] have been reported but emerging controversies regarding β-blockers in breast cancer need further evaluation [26-27,31]. Additional findings in this field are welcome. Nevertheless the development of HERG-blocker specific anticancer agentsand the use of verified cardiovascular drugs remain as important opportunities and the possibility of cardiovascular derivative HERG-blocker anticancer drugs is open [103] as well as the role of HERG-blockers facilitating chemotherapies [116–119,122]. Several risk factors, including electrolyte imbalance and polypharmacy with concomitant QT prolonging agent use can increase the risk of TdP in cancer patients [36,125], and separating the individual contributions of the various triggers for TdP remains problematic [125]. Indications and contraindications for cardiovascular drug use must always be respected as well as relative precautions. This translational impact will require certainly further evaluation but all efforts to expand the evidence base on cardio-oncology [126]can help to promote new strategies for patients' safety and to encourage patients in their heavy cancer journey.

Conflict of interest

The author reports no relationships that could be construed as a conflict of interest.

Acknowledgments

The author of this manuscript has certified that he adheres to the statement of ethical publishing as appears in International Journal of Cardiology.

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