PREDICTING CARDIAC RISK OF ANTI-CANCER DRUGS: A ROLE FOR HUMAN INDUCED PLURIPOTENT STEM CELL-DERIVED CARDIOMYOCYTES

Andrew Bruening-Wright, Leslie Ellison, James Kramer, Carlos A. Ojejo-Paz

ABSTRACT

Cardiotoxicity is a major complication of cancer therapy. It can occur after acute exposure to chemotherapeutic agents by direct effects on cardiac ion channels resulting in development of cardiac excitability and arrhythmias and ultimately heart failure. Current in vitro strategies for detecting these risks are arduous and often ineffective, particularly for those effects that occur over the course of days or weeks. This is particularly important when it is recognized that drugs may have direct effects on the synthesis and transport of channels to the membrane surface, mechanisms with half lives of many hours.

The CDI-CardioECR system allows for the recording of cardiac function and potential of signals of stimulated or spontaneously beating stem-cell derived cardiomyocytes (SC-D-CM). The main component of the impedance signal is the impedance threshold (I), see figure 3), a transient increase in electrode resistance that is obliterated by the region beyond which blockades. Three additional small impedance deflections are detected, two preceding the impedance threshold (IP and IN) and one occurring during repolarization (IP2). These findings are in good accordance with the previously reported deflection in IP2, suggesting that channel blockage is a reliable indicator of channel blockade. A future challenge will be the development of a device that can stimulate the cardiomyocytes and record the responses simultaneously.

METHODS

Data were analyzed using Origin, Matlab, and macros written in VBA. The output of the instrument is the cardiac excitation-contraction mechanisms targeted by anti-cancer drugs, and can be employed in de-risking strategies prior to clinical use. The Cardiotoxicity Induced by Drug Exposure (CDI) system detects acute and long-term TKI effects, predicts clinical cardiac risk, and may be a useful tool for rank-ordering and lead selection.

INTRODUCTION

Cardiotoxicity is a major complication of cancer therapy. It can occur after acute exposure to chemotherapeutic agents by direct effects on cardiac ion channels resulting in development of cardiac excitability and arrhythmias and ultimately heart failure. Current in vitro strategies for detecting these risks are arduous and often ineffective, particularly for those effects that occur over the course of days or weeks. This is particularly important when it is recognized that drugs may have direct effects on the synthesis and transport of channels to the membrane surface, mechanisms with half lives of many hours.

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RESULTS

Acute anticancer drug effects on field potential and impedance parameters are predicted by ion channel blocking potencies. These direct effects are a baseline to which long term effects on channels, likely the consequence of distinct modulatory processes, should be compared. The CDI-CardioECR system detects acute and long-term TKI effects, predicts clinical cardiac risk, and may be a useful tool for rank-ordering and lead selection.

1) The Field Potential and Impedance signals

2) Doxorubicin

3) Erlotinib

4) Lapatinib

5) Crizotinib

6) Sunitinib

CONCLUSIONS

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METHODS

We used the Cellogenesis RTCA Cardiotoxicity Assay (ACEA Biosciences) to record impedance and extracellular field potentials. Cardiomyocytes, from Cambrex BioScience (Walkersville, MD), were used as a source of cardiomyocytes. Each well contained 10^4 cardiomyocytes, which were seeded on a microelectrode array and cultured in EGM-2 medium (Cambrex Life Sciences, Walkersville, MD) supplemented with 10% FBS, 1% glutamine, 1% NEAA, and 1% antibiotic/antimycotic solution for 3 days. Cultures were maintained under a 95% air and 5% CO2 incubator at 37°C and were treated with anticancer drugs for 48 h. On the day before exposure, the cultures were treated with the compounds to be tested for an additional 12 h. The drug concentration was chosen based on the published literature.

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