Berberine associated to SGLT-2i exerts synergistic cardioprotective effects in cardiac cells exposed to the HER2-blocking agent Trastuzumab through pAMPK activation and reduction in Interleukin-6 levels


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PURPOSE

Trastuzumab has improved the prognosis in patients with HER2-positive breast cancer, but it can induce left ventricular dysfunction with reduced ejection fraction or HF during treatment. Dapagliflozin is a SGLT2i with cardio-renal benefits. In the DAPA-HF [Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure] trial, the sodium-glucose cotransporter 2 inhibitor dapagliflozin decreased the risk of worsening HF events and cardiovascular death in patients with HF and reduced ejection fraction. Berberine is a nutraceutical compound characterized by multiple metabolic effects in patients with/without cardiovascular diseases. Recent preclinical systematic review indicated that Berberine significantly reduces myocardial infarct size and the incidence of ventricular arrhythmia, improves cardiac function, ameliorates myocardial apoptosis. Here, we aimed to investigate on the potential cardioprotective properties of Berberine associated to SGLT2i Dapagliflozin against HER-2 blocking agent-induced cardiotoxicity.

METHODS

Human fetal cardiomyocytes (HFC cell line) were exposed to subclinical concentration of trastuzumab (200 nM) alone or co-incubated with Berberine (200 nM) or Dapagliflozin (50 nM) or both in combination for 48 h. After the incubation period, we performed the following tests: cell viability, apoptosis, expression of NLRP3 inflammasome, methylglyoxal and leukotrienes-B4. Expression of pAMPK was analyzed through western blot. Moreover, quantification of IL-6 was performed through ELISA method.

RESULTS

Trastuzumab induces apoptosis in human cardiac cells compared to untreated cells. Berberine and Dapagliflozin, associated to Trastuzumab, reduces apoptosis index. When combined, Berberine and Dapagliflozin, exerts a significant cardioprotective property, by reducing apoptosis in human cardiac cells exposed to Trastuzumab. MGL, a marker of glucose-mediated inflammation, was strongly enhanced after therapy with Trastuzumab. When combined to Berberine and Dapagliflozin, MGL expression was significantly reduced indicating glucose-mediated anti-inflammatory properties.

CONCLUSIONS AND CLINICAL PERSPECTIVES

Berberine and Dapagliflozin exerts significant cardioprotective effects in cardiac cells exposed to the HER2-blocking agent Trastuzumab. Berberine and Dapagliflozin in combination induces an anti-inflammatory phenotype to myocardial cells through the reduction of biomarkers involved in heart failure and apoptosis.