2021 ESMO congress

6MO
PCSK9 inhibitor evolocumab reduces cardiotoxicity and inflammation induced by doxorubicin-trastuzumab sequential treatment through MyD88/NF-kB/mTORC1 pathways

V. Quagliariello, S. Buccolo, M. Iovine, F. Cerrone, A. Paccone, N. Maurea

Background

Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) has emerged as a novel therapy to treat hypercholesterolaemia and related cardiovascular diseases. Evolocumab, a PCSK9 inhibitor, reduced the risk of cardiovascular events in patients with atherosclerotic cardiovascular diseases when added to maximally tolerated statin therapy (± ezetimibe), and recent data from the ODYSSEY OUTCOMES trial indicate that alirocumab added to maximally tolerated statin therapy (± other lipid-lowering drugs) reduces the risk of cardiovascular events in patients with a recent acute coronary syndrome.

Methods

Human fetal cardiomyocytes (HFC cell line) were exposed to subclinical concentration of doxorubicin, trastuzumab, sequential treatment of both (all 100 nM), alone or in combination with evolocumab (50 nM) for 48h. After the incubation period, we performed the following tests: determination of cell viability, through analysis of mitochondrial dehydrogenase activity, study of lipid peroxidation (quantifying cellular Malondialdehyde and 4-hydroxynonenal), intracellular Ca2+ homeostasis. Moreover, pro-inflammatory studied were also performed (activation of NLRP3 inflammasome; expression of TLR4/MyD88; mTORC1 Fox01/3a; transcriptional activation of p65/NF-κB and secretion of cytokines involved in cardiotoxicity (Interleukins 1β, 8, 6).

Results

Evolocumab co-incubated with doxorubicin alone or in sequence with trastuzumab exerts cardioprotective effects, enhancing cell viability of 35-43% compared to untreated cells ($p<0,05$ for all); Evolocumab reduced significantly the cardiotoxicity through MyD88/NF-KB/cytokines axis and mTORC1 Fox01/3α mediated mechanisms.

Conclusions

We demonstrated, for the first time, that the PCSK9 inhibitor evolocumab exerts direct effects in cardiomyocytes during doxorubicin and trastuzumab exposure turning on a new light on its possible use in cancer patients.

Legal entity responsible for the study

The authors.

Funding

Ministero della Salute, Italy.

Disclosure

All authors have declared no conflicts of interest.