ID: 01006
Type: Poster
Topic: Tumor biology

CM728, a novel naphthoquinone derivative that induces apoptosis in triple-negative breast cancer by increasing ROS and modulating multiple kinases

Elena Spínola[1] , Juan Carlos Montero[2] , Borja Guerra[1] , Roberto Jiménez[3] , José Quintana[1] , Francisco Estévez[1] , Leandro Fernández-Pérez[1] , Grant McNaughton-Smith[4] , Idaira Hueso-Falcón[4] , Manuel Rodríguez-López[4] , Nicolás Díaz-Chico[4] , Juan Carlos Díaz-Chico[1] , Atanasio Pandiella[2]

1) Instituto de Investigaciones Biomédicas y Sanitarias, Universidad de Las Palmas de Gran Canaria, España 2) Centro de Investigación del Cáncer, CSIC, Universidad de Salamanca, España 3) Instituto Canario de Investigación sobre el Cáncer, España 4) Centro Atlántico del Medicamento, España

Introduction:

Triple negative breast cancer (TNBC) represents an aggressive type of breast cancer characterized by the lack of expression of estrogen and progesterone receptors and the absence of the human epidermal growth factor receptor 2 (HER2) overexpression. Currently, combined chemotherapy is the treatment for TNBC, but it works in a small group of patients due to the heterogeneity of the disease. Thus, it is urgent to find more effective treatments against this tumor type. Naphthoquinones (NPQ) have positive effects against different human diseases. In particular, their antitumoral impact on several types of cancer is well documented. The Canary Islands pharmaceutical company, CEAMED, has synthesized new NPQ derivatives to be checked against human diseases.

Objectives:

Here, we summarize our study on the antitumoral effect of CM728, a new 1,4-NPQ derivative synthesized by CEAMED, on TNBC cell lines.

Methodology:

We used 3 TNBC cell lines: MDA-MB-231, Hs578T and BT549. Cell growth and viability was estimated by mitochondrial metabolization of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) and trypan blue staining. Cell cycle phases were analyzed by flow cytometry after the incubation with propidium iodide in the presence of RNAse. Apoptosis was estimated by subG1 phase and verified by annexin-V/propidium iodide double staining. Changes in phosphorylation and amount of proteins were analyzed by western blotting. Reactive oxygen species (ROS) were measured by flow cytometry after incubation with dichloro-dihydro-fluorescein diacetate (DCFH-DA).

Results:

CM728 produced an important decrease in mitochondrial activity in the 3 TNBC cell lines, with IC50 values around 100nM. This decrease in metabolic activity was due to a combination of growth inhibition and cell death. CM728 caused a dose and time-dependent increase in cells in the subG1 phase of cell cycle. In addition, the drug provoked cell cycle arrest in S and G2/M phases. These actions were associated with cleavage/increase in the activity of caspase-3,-8,-9, and cleavage of PARP and with increased of annexin V-positive cells. CM728 also increased the double-strand DNA break marker γH2AX. Moreover, CM728 showed multikinase modulatory effects through increased JNK, p38-MAPK, Akt, and Erk1/2 phosphorylation, and decreased Stat3 phosphorylation. Interestingly, CM728 caused an early increase in ROS, an effect that

was counteracted by the antioxidant N-acetyl-L-cysteine (NAC). Furthermore, in the presence of NAC, the influence of CM728 on JNK and p38-MAPK phosphorylation was attenuated.

Conclusions:

Our data suggest that CM-728, a ROS and multikinase modulator, presents antitumoral activity against TNBC cells, raising the possibility of exploring its clinical use.

[files191=2;500;500][fileShow][/files]