

Elesclomol and chemotherapy agents synergistically induce apoptosis in breast cancer cells

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Abstract

Background:

Elesclomol is an investigational agent that selectively increases oxidative stress in cancer cells to induce apoptosis. Elesclomol plus paclitaxel was shown to prolong progression-free survival compared with paclitaxel alone in a Phase 2 clinical trial in patients with metastatic melanoma. Currently, the mechanism underlying the synergy between elesclomol and paclitaxel is under investigation.

Methods:

MCF-7, MDA-MB-231, and HCC1806 human breast cancer cells and normal breast epithelial cells were treated with elesclomol or with elesclomol plus doxorubicin or paclitaxel. Cell growth was measured by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. Apoptosis was assessed by Annexin V and propidium iodide double staining followed by flow cytometry. Elesclomol-activated stress and survival signaling proteins and their involvement in cell growth were analyzed by western blotting, flow cytometry, and a human apoptosis-related protein array. All statistical tests were two-sided.

Results:

Elesclomol alone modestly inhibited growth of breast cancer cells but not normal breast epithelial cells. Elesclomol plus doxorubicin or paclitaxel synergistically induced apoptosis and suppressed growth of cancer cells. While both c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase were activated by elesclomol, only JNK was involved in the apoptosis induction by elesclomol. This apoptosis was associated with increase of cleaved caspase-3, p21^{Cip1}, and p27^{Ink4}, and decrease of the inhibitor of apoptosis proteins. Surprisingly, Akt/Hsp70 survival signaling was also strongly induced by elesclomol, which may reflect a cellular feedback mechanism. Blockade of Akt activation using a small molecule inhibitor enhanced elesclomol-elicited apoptosis.

Conclusions:

Elesclomol significantly increases the cytotoxic effect of doxorubicin or paclitaxel in breast cancer cells. Clinical trials of elesclomol in combination with chemotherapy drugs in breast cancer may be warranted. In addition, Akt may be targeted to render cancer cells more sensitive to elesclomol.

Results

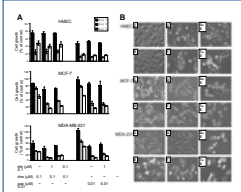


Figure 1. Effect of elesclomol in combination with doxorubicin or paclitaxel on the growth of breast cancer cells and HMEC.

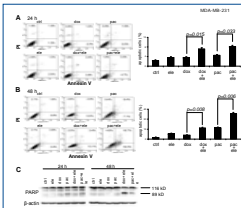


Figure 2. Effect of elesclomol in combination with doxorubicin or paclitaxel on cell apoptosis.

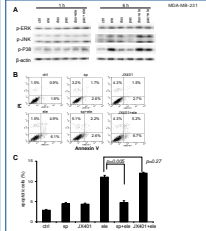


Figure 3. JNK mediates the elesclomol effect on cell apoptosis.

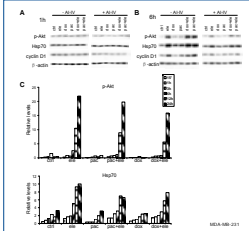


Figure 4. Elesclomol induces Hsp70 and cyclin D1 via Akt.

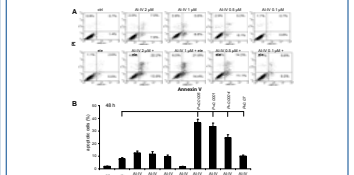


Figure 5. Akt inhibition increases elesclomol-induced cell apoptosis.

Abbreviations
 C: control
 E: elesclomol
 D: doxorubicin
 T: paclitaxel
 D+E: doxorubicin plus elesclomol
 T+E: paclitaxel plus elesclomol
 AI-IV: AKT inhibitor

Summary

1. Elesclomol potentiates the sensitivity of breast cancer cells to chemotherapy drugs
2. Elesclomol increases chemotherapy drug-induced apoptosis in breast cancer cells
3. JNK may play a role in apoptosis induced by elesclomol
4. AKT may be responsible for Hsp70 and cyclin D1 induction
5. Akt inhibition enhances the effect of elesclomol on breast cancer cell growth

Conclusions

1. Combined elesclomol with cytotoxic chemotherapeutic agents induce apoptosis in breast cancer cells via c-Jun N-terminal kinase (JNK) signaling and downregulation of survival proteins.
2. Exploiting ROS may represent a novel approach in combination with cytotoxic chemotherapies and/or survival pathway-targeted therapies.