

β -caryophyllene and low-doses of doxorubicin against liver cancer cells: a “metronomic chemotherapy”

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Cholangiocarcinoma and hepatocellular carcinoma are primary liver cancers, both representing a growing challenge due to their increasing morbidity and mortality. A “metronomic chemotherapy”, consisting of the repeated administration of low and/or continuous doses of anti-neoplastic drugs, represents an alternative approach to the standard chemotherapy [1]. Numerous natural substances exhibited *in vitro* chemosensitizing features: in particular, the natural sesquiterpene β -caryophyllene (CRY) has been proved to increase the cytotoxicity of doxorubicin (DOXO) in leukemic cells [2]. Hence, our aim has been to evaluate the ability of CRY to enhance the efficacy of low-dose DOXO in human liver cancer cells, by applying a metronomic protocol. To this end, human liver HepG2 and CCA cells have been used as models of hepatocellular carcinoma and cholangiocarcinoma. The metronomic protocol was based on a 2h low-time exposition to the test substances, followed by 72h incubation for restoring. This scheduling has been applied 3 times and cytotoxicity was measured by MTT assay. Both the substances alone (CRY 1-100 $\mu\text{g}/\text{ml}$; DOXO 1-500 $\mu\text{g}/\text{ml}$) and the combination of DOXO with a nontoxic concentration of CRY were assessed. We found that the repeated treatments with low concentrations produced a significant potentiation (about 30 %) of DOXO cytotoxicity in HepG2. The combination with CRY increased the DOXO activity, reaching a 70 % inhibition of cell viability at 50 $\mu\text{g}/\text{ml}$ after 2 repeated treatments. Similar effects were found in CCA, although repeated treatments induced no additional potentiation. These results highlight a possible role of CRY as a chemosensitizing agent for DOXO-based chemotherapy of liver cancer.

References

- [1] Riganti et al. (2015) Two repeated low doses of doxorubicin are more effective than a single high dose against tumors overexpressing P-glycoprotein. *Cancer Lett.* 360(2): 219-226.
- [2] Di Giacomo et al. (2017) Chemosensitizing properties of β -Caryophyllene Oxide in combination with Doxorubicin in human cancer cells. *Anticancer Res.* 37(3): 1191-1196.

Keywords

Cholangiocarcinoma, hepatocellular carcinoma, CRY, doxorubicin