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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 μg/ml; DOXO 1-500 μg/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 μg/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

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Keywords
Cholangiocarcinoma, hepatocellular carcinoma, CRY, doxorubicin