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TITOLO RELAZIONE: Chemosensitizing effect of the natural product voacamine.

ABSTRACT: Most of the tumors may show both *in vitro* and *in vivo*, a lack of sensitivity to chemotherapeutic agents, thus to be hardly attacked with conventional drug treatments. One of the main goals of cancer research is therefore to identify new therapeutic strategies effective against drug resistant tumors. To this end, numerous natural products of different origin and chemical structure were used, either alone or in combination with conventional anticancer drugs, hoping to inhibitor at least reduce, the drug resistance of cancer cells.

The phenomenon of drug resistance (MDR: multidrug resistance) is often due to the ability of tumor cells to extrude cytotoxic agents by reducing their intracellular concentration. In this complex mechanism, a very important role is played by the transport molecule P-glycoprotein (P-gp) which is generally overexpressed on the surface of MDR cells.,. We have previously shown that the bisindolic alkaloid voacamine, isolated from the plant *Peschiera fuchsiaefolia*, is able to exert a marked chemosensitizing effect on drug-resistant tumor cells treated with doxorubicin. The resistant cells pretreated with voacamine show an increased intracellular accumulation of the drug, mainly localized within the nucleus such as in the sensitive counterpart. The analysis of cell survival and observations of optical and electron microscopy show a significant increase in the cytotoxic effect of doxorubicin against resistant cells pretreated with the plant extract. We have subsequently shown that voacamine is able to exert such effects as a substrate for P-gp and thereby acting as a competitive antagonist against chemotherapeutic agent.

During this research, some experimental evidences have suggested that the voacamine induced its cytotoxic effect by using autophagic mechanism.

Numerous studies, both in vitro and in vivo, support the hypothesis that different programs of death can be triggered depending on the cellular stress induced. Autophagy is a process that is induced in response to different cytotoxic stimuli. This process may protect cancer cells from apoptosis after treatment with anticancer drugs or be a mechanism of death for cells that have a shortfall in their apoptotic program. The first goal of this study was to examine the presence of intracytoplasmic vacuoles acidic by vital dyes such as acridine orange (AO) and monodansilcadaverina (MDC). The evaluation was performed by light confocal microscopy and quantification by flow cytometry. The MDC dye, fluorescent marker specific for the presence of autophagolysosomes (organelles containing lysosomal enzymes, acid phosphatase and mature forms of cathepsin D) revealed an increase in the percentage of autophagosomal structures in the MDR cell lines, after 24 hours of voacamine treatments. In addition, observations by transmission electron microscopy revealed, in resistant cells treated with voacamine, either alone or in combination with doxorubicin, the presence of numerous vacuoles surrounded by double membrane with inside cytoplasmic organelles degenerate s.

In view of the dual role of autophagy in cancer cells (either protective or lethal, either pro- or anti-apoptotic), our findings showed that a natural product able to induce autophagy could be effective against drug resistant tumors in vitro, either used alone or in association with conventional chemotherapeutics. The application of quantitative pharmacology (QP), a multidisciplinary approach to drug discovery and development, represents the next iteration of a model-based approach for voacamine in different tumors.

Bibliografia

Meschini S. et al. *Int. J. Oncol.* 2003; 23:1505-13
Meschini S. et al. *Int. J. Oncol.* 2005; 27:1597-1603
Meschini S. et al. *Toxicol. in Vitro*, 2007; 21:197-203
Meschini S. et al. *Autophagy* 2008; 4:1020-33
Meschini S. et al. *Curr. Cancer Drug Ther.*, 2011,11, 357-359.