LIPOSOMAL FORMULATION OF \( \alpha \)-TOCOPHERYL MALEAMIDE: IN VITRO AND IN VIVO TOXICOLOGICAL PROFILE AND ANTICANCER EFFECT AGAINST SPONTANEOUS BREAST CARCINOMAS IN MICE

Turánek, J., Turánek-Knotigová, P., Koudelka, Š., Vacek, A., Salvatore, B. A. & Neužil, J.
VÚVeL, Brno, Czech Republic

Abstract
The vitamin E (VE) analogue \( \alpha \)-tocopheryl succinate (\( \alpha \)-TOS) is an efficient anti-cancer drug. Improved efficacy was achieved through the synthesis of \( \alpha \)-tocopheryl maleamide (\( \alpha \)-TAM), an esterase-resistant analogue of \( \alpha \)-tocopheryl maleate. In vitro tests demonstrated significantly higher cytotoxicity of \( \alpha \)-TAM towards cancer cells (MCF-7, B16F10) compared to \( \alpha \)-TOS and other analogues that are prone to esterase-catalyzed hydrolysis. However, in vitro models demonstrated that \( \alpha \)-TAM was cytotoxic to a variety of non-malignant cells (e.g. lymphocytes and bone marrow progenitors). Thus we developed lyophilised liposomal formulations of both \( \alpha \)-TOS and \( \alpha \)-TAM to solve the problem with cytotoxicity of \( \alpha \)-TAM, as well as the low solubility of both drugs. These formulations were tested in various mouse cancer models (hollow fiber implants, spontaneous breast carcinomas). Remarkably, no acute toxicity nor immunotoxicity were detected with the in vivo liposomal formulations of \( \alpha \)-TAM, and yet this formulation significantly reduced the growth of cancer cells in hollow fiber implants (50-70% reduction of growth). Moreover, liposomal formulation of \( \alpha \)-TAM and \( \alpha \)-TOS each prevented the growth of tumours in transgenic FVB/N c-neu mice bearing spontaneous breast carcinomas. Liposomal formulation of \( \alpha \)-TAM demonstrated anti-cancer activity both in vitro and in vivo at 1/10 the concentration of comparable \( \alpha \)-TOS formulations. Thus, the liposomal formulation of \( \alpha \)-TAM preserved its strong anti-cancer efficacy while eliminating the in vivo toxicity found of the free drug applied in DMSO. Liposome-based targeted delivery systems for analogues of vitamin E are of interest for further development of efficient and safe drug formulation for clinical trials.

Acknowledgement: This work was supported by grants: grant No. MZE 0002716202 and KAN 200520703 AVČR

Author did not supply full text of the paper/poster