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STRATEGIES TO ENHANCE RADIOSENSITIVITY AND CHEMOSENSITIVITY

Within the Division of Experimental Therapy, our group conducts two projects. The first focuses on inhibitors of DNA repair as radiosensitizers (collaboration with Conchita Vens). The NAD+-depleting agent APO866 was found to enhance radiation-induced cell death and act as a radiosensitizer in various models, including two prostate cancer cell lines. Restoration of cellular NAD levels abolished the cytotoxic effect. In vivo MTD of APO866 was defined. PARP inhibitors are also good candidates for combined use with DNA damaging agents. The main mechanism by which both radiation and cisplatin kill tumor cells is by an accumulation of un- or misrepaired DNA damage. PARP inhibitors increase radiation and chemotherapy (Cisplatin) response in preclinical studies. PARP inhibitors have been shown to specifically kill homologous recombination deficient tumor cells as single agents. We have designed 3 phase I-II studies evaluating the safety and tolerability of Olaparib in combination with (cisplatin-based chemo-) radiotherapy in locally advanced breast cancer, NSCLC and head and neck cancer. Olaparib exhibits low systemic toxicity profiles when given as monotherapy. When combined with chemotherapeutic agents more toxicity is seen.

In a second project we investigate the patented concept of improved drug delivery by short chain sphingolipid-enriched liposomes in vitro and in vivo. We examined this novel concept of GC-directed membrane permeabilization for doxorubicin in a spontaneous mouse tumor model that mimics human Invasive Lobular Carcinoma (ILC) breast cancer. We found that GC-enriched liposomal doxorubicin enhanced the uptake of doxorubicin in ILC cell cultures at least five-fold, and inhibited tumor outgrowth in vivo much more effectively than either of the two clinically applied formulations of doxorubicin, (free, non-liposomal) Adriamycin® or (standard/ conventional liposomal) Caelyx®. Mice treated with GC-liposomal doxorubicin showed an extended overall survival (up to 2-fold) compared with conventional liposomes. No increase in normal tissue toxicity was observed upon the addition of GC. These data hold promise for widening the therapeutic window of amphiphilic anti-cancer agents, including doxorubicin, using this plasma membrane modulation strategy. We are currently continuing the GC-enriched liposomal doxorubicin towards clinical investigations.

Publications

Van Lummel M, Van Blitterswijk WJ, Vink SR, Veldman RJ, Van der Valk MA, Schipper D, Dicheva BM, Eggermont AMM, ten Hagen TLM, Verheij M, Koning GA. Enriching lipid nanovesicles with short-chain glucosylceramide improves doxorubicin delivery and efficacy in solid tumors. The FASEB Journal 2010 (in press)

Verheij M, Vens C, Van Triest B. Novel therapeutics in combination with radiotherapy to improve cancer treatment: Rationale, mechanisms of action and clinical perspective. Drug Resist Update 2010;13:29-43