Revisiting the use of sPLA2-sensitive liposomes in cancer therapy

The first developed secretory phospholipase A2 (sPLA2) sensitive liposomal cisplatin formulation (LiPlaCis®) is currently undergoing clinical evaluation. In the present study we revisit and evaluate critical preclinical parameters important for the therapeutic potential and safety of platinum drugs, here oxaliplatin (L-OHP), formulated in sPLA2 sensitive liposomes. We show the mole percentage of negatively charged phospholipid needed to obtain enzyme-sensitivity for saturated systems is ≥ 25% for 16-carbon chain lipid membranes, and > 40% for 18-chain lipid membranes, which was surprising as 25% is used clinically in LiPlaCis®. Efficient sPLA2-dependent growth inhibition of colorectal cancer cells was demonstrated in vitro, where cell membrane degradation and cytolsis depends on the sensitivity of the formulation towards the enzyme and is governed by the amount of lysolipids generated and the presence of serum proteins. We found that serum proteins did not affect the lipase activity of the enzyme towards the membranes but instead sequester the lysolipid byproducts consequently inhibiting their detergent-like cytotoxic properties. In vivo therapeutic potential and safety of the liposomes was investigated in nude mice bearing sPLA2-deficient FaDu squamous carcinoma and sPLA2-expressing Colo205 colorectal adenocarcinoma. After intravenous injections, the tumor growth was suppressed for liposomal L-OHP relative to free drug, but only a weak response was observed for slow- and fast-releasing sPLA2-sensitive formulations compared to non-sensitive liposomes. Also, the mice did not show longer survival. In turn, for the highly sPLA2-sensitive liposomes, multiple high doses caused petechial cutaneous hemorrhages, along with multifocal hepatonecrotic lesions, suggestive of premature activation in skin and liver irrespective of sPLA2-status of the tumor engraft. These results indicate that although liposomal carriers can improve the antitumor efficacy of platinum drugs, sPLA2-triggered release suffers from a narrow therapeutic index and has safety concerns.

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