Cover Story

PK/PD model for liposomal chemophototherapy

Photodynamic therapy (PDT) has been clinically approved as a treatment option for local ablation of several solid tumor types [1]. PDT involves the administration of a photosensitizer followed by light irradiation of target site(s). Chemotherapy, which is used to treat advanced cancer patients, has been combined with PDT in pre-clinical and clinical studies. The combination of chemotherapy and PDT, or chemophototherapy (CPT), can be complex, as the separate combination of a photosensitizer and chemotherapy agents has many different possibilities and timings. To simplify CPT, numerous groups have developed integrated agents, which incorporate both chemo- and photo- therapy components into a single formulation.

Porphyrin-phospholipid (PoP) liposomes contain PoP, a photosensitizer-lipid conjugate that stably embeds in the lipid bilayer and can trigger release of encapsulated cargos [2]. Doxorubicin (Dox) can be loaded into a sterically-stabilized PoP liposome formulation, resulting in a stable liposome formulation (long-circulating Dox in PoP liposomes, or "LC-Dox-PoP") [3]. The nearly identical long circulation times of the PoP and Dox component of LC-Dox-PoP reflect the high blood stability of the liposomes [4]. Significant enhancement of drug accumulation after laser treatment has been observed in numerous rodent tumor models, resulting in potent tumor ablation [3,4].

Successful translation of CPT likely requires a quantitative understanding of pharmacokinetics and pharmacodynamics (PK/PD) of the therapy modality. In this issue, Professor Jonathan Lovell and his team present a semi-mechanistic PK/PD model to characterize the pharmacokinetics, tumor drug distribution, and anti-tumor efficacy [5]. The model is based on enhanced Dox influx and efflux rates into the tumor, which were measured following laser treatment. The two-compartment PK/PD model accurately predicted drug content in light-treated tumors. The PK/PD model was limited to light-treatments that were carried out shortly after liposome administration, since in that scenario, vascular permeabilization induced an increase in tumor Dox biodistribution that could be measured over time. This PK/PD model was developed in a single tumor model, and therefore, will benefit from future testing in different tumor types and in larger animals.

Despite the promising preclinical results of many formulations based on liposomes, polymer micelles, and other nano-scale delivery systems, few have had successful transition to clinical successes [6]. For example, thermo-sensitive liposomes have been investigated clinically in combination with thermal tumor ablation, but did not meet the primary endpoint in a phase III trial for liver cancer (ClinicalTrials.gov ID: NCT00617981). One of the potential reasons was that heat activated-liposomes tend to have relatively limited serum stability, limiting longer-term drug uptake in tumors [7]. The pharmacokinetics of LC-Dox-PoP liposomes are similar to FDA-approved Doxil, thus bypassing serum stability concerns. However, thermal ablation of tumors is well-established, whereas light delivery to tumors is not as widely implemented. Efficient delivery of light into tissues is a major challenge for successful translation of any light-based tumor treatment, as light penetration is limited to less than a couple of centimeters. The light-sensitive liposomes may show efficacy in mouse models, as thermo-sensitive liposome formulations did. The big question is whether these environment-sensitive liposome formulations behave similarly in the human body where the tissue mass and the blood volume are orders of magnitude larger than those in a mouse. The impacts of such drastic differences can be studied using the PK/PD models that can be applied to humans. The study by the Lovell team provides a good starting point in rationale translation from the mouse experiments to clinical studies.

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