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Cover story

Sustained efficacy of paclitaxel nanocrystals in hydrogel depot

Intraperitoneal (IP) chemotherapy has been pursued as a promising post-surgical therapy of peritoneal carcinomas. Several clinical studies suggest therapeutic benefits of IP chemotherapy compared with intravenous therapy [1], which led to an endorsement of the National Cancer Institute for IP chemotherapy for patients with optimally resected stage III ovarian cancer. Despite the clinically-proven advantages, IP chemotherapy has not become a routine component of ovarian cancer treatment, due to the increased time and effort requirement and the treatment-related complications. This is a challenge partly stemming from the inability to maintain effective drug concentration in the peritoneal cavity, which necessitates large volume infusions and indwelling catheters, causing pressure-associated pain and catheter infection. A drug delivery system that can attenuate the drug release and its systemic absorption would help relieve this challenge by reducing the dose requirement and frequency; however, this opportunity has not been explored extensively.

In this issue, Professor Yoon Yeo and her colleagues report the development of a hydrogel depot of paclitaxel nanocrystals (PNC) and its use in IP chemotherapy of ovarian cancer [2]. In their previous work, they reported the difficulty in controlling the dissolution of paclitaxel loaded in a hydrogel and its limited effectiveness on IP tumors [3]. The present study overcomes the challenge by preformulating paclitaxel in a nanocrystal form, which can show a greater dissolution rate than uncontrolled precipitates due to the high surface area to volume ratio. PNC with a z-average of 260 nm was prepared by the anti-solvent and temperature-induced crystallization method, loaded in a hydrogel precursor, and injected IP to mice with peritoneal tumors. The high cytotoxicity of PNC and low maximum tolerated dose of PNC-gel relative to microparticulate counterparts indicate greater availability of paclitaxel to tumor cells, mainly due to the improved dissolution. A single IP injection of PNC-gel attenuated the growth of tumors and prolonged the survival of tumor-bearing mice significantly better than other formulations including Taxol, demonstrating the benefit of prolonged drug retention in local chemotherapy of IP tumors.

Although the nanoparticle formulation showed improved efficacy, the authors are yet to investigate whether PNC has maintained the particle size within the degrading hydrogel to preserve the enhanced paclitaxel solubility. It is also curious whether further reduction of particle size will enhance therapeutic efficacy of the depot system even more. In the continued quest for optimal formulation of paclitaxel, the authors make an intriguing note about *in vitro* drug release studies. They previously reported challenges in studying the release kinetics of poorly water-soluble drugs, such as paclitaxel, and the risk of underestimating the drug release during *in vitro* experimental condition [4]. Additional challenges are encountered in evaluating dissolution of nanocrystals, which are prone to aggregation or adsorption during traditional sampling processes such as centrifugation or dialysis. The challenges aggravate when amphiphilic nature and limited volume of the peritoneal fluid are considered.

Given difficulties in correlating the *in vitro* release kinetics and *in vivo* outcomes, i.e., *in vitro-in vivo* correlation (IVIVC), the authors rightfully ask whether the current methods of studying *in vitro* release kinetics has any practical value. The current methods do not reflect, even remotely, the physiological complexity, and thus, the results may have little value in predicting *in vivo* performance of a drug carrier. This critical question has been present all along, but it has been conveniently ignored by many researchers in the field. Many *in vitro* evaluation methods have become a tradition without rigorous validation. The *in vitro* drug release kinetics has little value, if it only belies *in vivo* efficacy. It is time to revisit conventional *in vitro* models used to evaluate drug delivery systems and invest in new methods with improved IVIVC. In a bigger picture, it is also time to revisit conventional small animal models to find a better way to correlate the experimental data to clinical efficacy. The limited clinical data makes it very difficult to achieve the goal, but continuing the same old small animal models will certainly not provide an answer.

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