Innovative Irinotecan-Loaded Nanomicelles Will Enter Phase I Clinical Trial in 2021

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Recent progress at the National Center for Nanoscience and Technology of China has enabled an extremely facile method to encapsulate irinotecan (CPT-11) into micelle-based nanoparticles (named as IH-NM). In preclinical study, compared with free CPT-11, IH-NM exhibited 1.56-fold higher maximum tolerance dose (MTD), ~2.45-fold higher antitumor efficacy at 80% of MTD dosage, higher plasma exposure, and slower clearance from the plasma. The IH-NM technology received Clinical Trial Permission from the National Medical Products Administration (NMPA) of China on Mar 6, 2019. The Phase I clinical trial is under preparation.

KEY FINDING

IH-NM was produced by innovatively co-dissolving the active pharmaceutical ingredient and an amphiphilic excipient in a water-based system. In preclinical study, IH-NM improved maximum tolerance dosage (MTD) by 1.56-fold, and exhibited 2.45-fold higher antitumor efficacy at 80% of MTD, higher plasma exposure, and slower clearance from plasma than irinotecan (CPT-11).

TRANSLATIONAL

Chemotherapeutic drugs formulated via nanotechnology (e.g., Doxil, Abraxane) have entered the clinic and have benefited cancer patients globally. Given the success of these drugs, significant research efforts are pushing similar technologies further, by seeking more advantages over currently approved drugs. For example, many of the nanoparticle systems in clinical trials use synthetic polymers as excipients to form micelles. Recent progress at the National Center for Nanoscience and Technology of China has enabled an extremely facile method to load CPT-11 into micelle-based nanoparticles. Preclinical study showed greatly improved antitumor efficacy over the normal CPT-11 formulation.

Colorectal cancer (CRC) is the third most common cancer and is the second leading cause of cancer-related deaths worldwide.1 According to the global cancer statistics, approximately 1.8 million cases and 881,000 deaths related to CRC occurred worldwide in 2018.2 Although 5-year survival rates have been improved for stage I or II CRC patients, 5-year survival rates of metastatic CRC patients remain low. Irinotecan is one of the most extensively used cytotoxic chemotherapeutic drugs for treating CRC in the clinic. Irinotecan is a semi-synthetic derivative of camptothecin, which can suppress tumor proliferation through inhibition of DNA Topoisomerase I.3,7 Irinotecan in combination with 5-fluorouracil/leucovorin (5FU/LV) is currently recommended in the United States and Europe as first-line therapy for metastatic CRC.3 Unfortunately, the maximum potential effect of CPT-11 has been limited by systemic toxicity and low tolerability in patients.

In an attempt to improve the efficacy of CPT-11 while mitigating its side effects for treatment of CRC, we have developed a novel method to incorporate CPT-11 into a micelle system and produced IH-NM micelles. Unlike previous techniques for manufacturing nanoparticles, including microemulsions, liposomes, emulsion/solvent evaporation, and nanoprecipitation, our method produces them by co-dissolving the active pharmaceutical ingredient and the amphiphilic excipient in a water-based system. Due to migration of the dissolved drug to the preformed micelle core, dissolution of the drug is continuously driven forward. This technique requires precise matching of the solubility of the active pharmaceutical ingredient and critical micelle concentration of the excipient. In order to facilitate fast approval by regulatory agencies, we tested a series of Food and Drug Administration-approved materials and found that (1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)2000]) (DSPE-PEG2000) can form nanoparticles with CPT-11 under carefully optimized formulations. The prepared CPT-11-loaded micelles have a hydrodynamic diameter of 12.34 ± 0.07 nm, with a polydispersity index of 0.192 ± 0.015. The diameter measured by transmission electron microscopy is ~10 nm (Figure 1A). The encapsulation efficiency and drug loading efficiency are as high as 92.3% and 18.1%. Other nanoparticle fabrication techniques that encapsulate chemotherapeutics, such as liposomes, emulsions, and nanoprecipitation, typically achieve no more than 14 wt% drug loading. In addition, this extremely simple physical process can be adapted to a good manufacturing practice-compliant facility, which is required for large-scale pharmaceutical production. Many nanoparticle fabrication techniques have failed to enter clinical trials because the laboratory equipment used to develop the technology is not available in a commercial production setting. For clinical trial, we aim to further scale up the production capacity from 2 L to 100 L per batch. In the future, this technique can be scaled to meet potential global manufacturing needs.

This nanoparticle formulation of CPT-11 altered the way the drug interacts with blood components and therefore allows for enhanced tolerability, which is highlighted in our preclinical study in mice. The MTD of free CPT-11 and IH-NM drug was determined in BALB/c nude mice bearing tumors derived from the human colon carcinoma cell line COLO205. The MTD of free CPT-11 was found to be 276.5 mg/m², while the MTD of IH-NM was found to be 432.0 mg/m². Therefore, the MTD of the IH-NM was ~1.56-fold higher than that of the free drug (Figure 1B). This indicated that the micelle-based encapsulation strategy significantly decreased the systemic toxicity of irinotecan.

Efficacy was evaluated in a COLO205 subcutaneous xenograft mouse model. Mice were administered with free CPT-11 or IH-NM via tail vein injection (n = 8/group). Each mouse received three injections, once a week for 3 weeks. To avoid toxicity caused by multiple dosages, mice received doses that were 80% and 64% of the MTD. At both doses, mice receiving IH-NM had statistically lower mean relative tumor volume (T/C) than mice receiving free CPT-11 at day 21. The antitumor efficacy for IH-NM was better than that of free CPT-11 at 80% of MTD dosage (Figure 1C). Body weights of mice in all groups remained stable during the experiment. No hematological toxicity and no obvious pathological changes in the main organs were observed in any of the mice. The anti-tumor efficacy for IH-NM was ~2.45-fold (average value of two sets of animal experiment) higher than that of free CPT-11 at 80% of MTD dosage.

Furthermore, pharmacokinetic profiling in a canine model revealed that IH-NM had 1.19-fold higher plasma exposure as measured by area under the curve compared with free CPT-11. The IH-NM exhibited lower clearance,
longer t1/2 and longer mean residence time than free CPT-11. The differences were statistically significant, which demonstrated that IH-NM is cleared more slowly from plasma. These results indicated that the nanoparticle functioned as a “drug sponge,” releasing CPT-11 slowly in the bloodstream and thus achieving higher tolerability and lower toxicity.

In conclusion, we have developed a novel technology to effectively encapsulate CPT-11 into nanomicelles formed from DSPE-PEG2000. The production capacity can be scaled up to meet potential clinical needs under regulatory compliance. We have demonstrated that the MTD was increased by 50% when CPT-11 was encapsulated within our nanoparticle system, which indicates that our formulation decreases systemic toxicity. With improved tolerability, mice could receive a 1.56-fold higher CPT-11 dose with IH-NM than with the free drug, resulting in substantially better efficacy in the preclinical model. Further work is being conducted to more thoroughly understand the mechanisms behind the improved tolerability and reduced toxicity.

The IH-NM technology received Clinical Trial Permission from NMPA of China on Mar 6, 2019 (CXHL1700025). The Phase I clinical trial will begin in 2021.

**PATENT NUMBER**

This IH-NM technology has been authorized as an invention patent in China (No. 1836159).

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**DECLARATION OF INTERESTS**

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