Improved Therapy of Colorectal Cancer with Camptothecin-Loaded Silica Nanoparticles: A Preclinical Study

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Abstract

Introduction: Although silica nanoparticles (MSN) have found application for the delivery and controlled release of small therapeutic molecules [1-3], very few studies report on the performance of silica-based nanodrugs at the preclinical stage [4,5]. Here, we demonstrate that surface-modified silica nanoparticles loaded with camptothecin (SNP-CPT) show high therapeutic efficacy and biocompatibility in human colorectal cancer xenografts.
Methods: Amorphous silica nanoparticles (10 nm average diameter) with the drug linked by ester bond at the 20-OH position were prepared as reported [6]. A human subcutaneous colorectal mouse model was used for the tolerability and efficacy studies. For this purpose, HT-29.Fluc cells were subcutaneously injected on the rear right flank of mice (female athymic nude mice, Harlan) and tumor growth was monitored twice a week for 22 days by conventional caliper measurements. During this time, tumor-bearing mice were treated intravenously with 0.8 mg CPT equivalent/kg twice a week. The toxicity of the compounds was determined by monitoring the animal's body weight (T/C ratio), eating and physical activity results [4,7].
Results and discussion: The treatment with naked CPT induced dose-dependent severe toxicities such as pain, hematuria, necrosis and partial loss of the tail. In contrast, the administration of SNP-CPT colloids did not induce any damage in the animals. The nanodrug accumulated preferentially in tumor by EPR effect [8], inducing a more effective tumor growth delay than naked CPT (Fig. 1). This may be due to the slow release of the drug from SNP-CPT in the tumor tissue, as the acidification within the lysosomes may stabilize the ester linkage, providing a slow release mechanism for the active drug that allows for a long-term therapeutic effect [9].
Conclusion: Colloids of silica constitute a novel drug delivery system for CPT that imposes improved tumor growth inhibition than naked drug and shows no toxicity, thus widening the therapeutic window of current alkaloid anticancer treatments.

References

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Figures

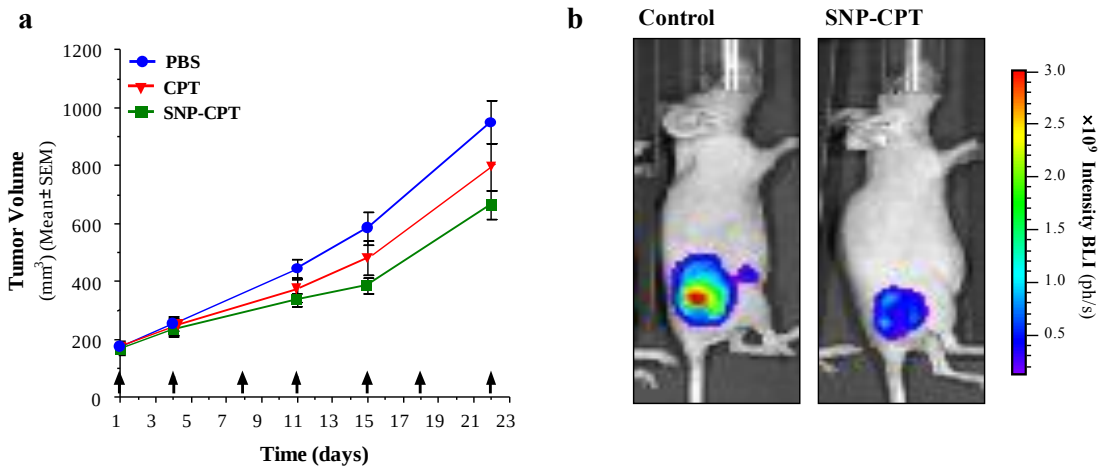

Fig. 1 a) Growth inhibition curves of the localized subcutaneous HT-29.Fluc colorectal cancer tumors in athymic nude mice treated with CPT or SNP-CPT. For comparison, a control administrated with PBS is also shown. Vertical arrows indicate points of drug injection; b) *In vivo* evolution of tumor HT-29.Fluc in athymic female mice (day 22 of treatment) by bioluminescence image. Left: the control was administered saline solution. Right: mouse received two injections per week of a SNP-CPT suspension in saline solution, corresponding to a 0.8 mg CPT/kg dose. Significant tumor recession and necrosis in the SNP-CPT treated mouse can be observed.