Enhanced paclitaxel delivery to tumors using a new lipid nanocapsule-based formulation

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Introduction

PTX-LNC (paclitaxel, PTTX), one of the first microtubule stabilizing agents, is among the most widely used chemotherapy agents in various cancers, especially ovarian and breast cancer. However, because of its poor water-solubility, PTX must be dissolved in ethanol and Cremophor® EL. Cremophor® EL has been proven to be associated with a number of severe side effects, including hypersensitivity, neurotoxicity and dramatic allergic reactions. These side effects are a major limitation in the use of PTX in the clinic.

To avoid these side effects, there is a need to develop alternative formulations of PTX with better aqueous solubility and reduced risk of associated serious adverse effects. In this study, PTX was formulated to lipop Nanocapsule (LNC), prepared into the phase inversion temperature method. The pharmacokinetics/pharmacodynamic (PK/PD) parameters of PTX-LNC were evaluated in a BALB/C nude mouse model bearing human ovarian tumor implanted subcutaneously.

Material and Methods

PTX-LNC
Composition: Solutol® HS 15 (15), Pluronic® F-108 (15), Lipoid® (15) (Sigma-Aldrich, St Louis, MO), Captex (Mallinckrodt, Inc., Athes, France), distilled water at pH 7.4.

In vivo studies
Preparation of LNC
PTX-LNC was prepared by the phase inversion temperature method in a water-bath at 4°C using a so-called cone plate viscometer (Rea 3). The phase inversion temperature method consists in preparing the LNC with water phase in a cone plate viscometer at 4°C. The cone temperature is increased from 3°C to 27°C at a constant rate of 1°C/minute. The cone phase temperature at which the LNC viscosity suddenly increases is defined as the phase inversion temperature (MIT). The LNC is then stored in the water-bath at 4°C before being used.

Preparation of PTX-LNC
PTX-LNC was prepared by dissolving PTX (1.3 mg) in a mixture of solvents (Solutol® HS 15 (15), Pluronic® F-108 (15), Lipoid® (15), Captex (Mallinckrodt, Inc., Athes, France) at pH 7.4) and adjusting the final concentration of PTX to 13.2 μg/ml. The solution was then freeze-dried and reconstituted with saline to obtain a concentration of 12 mg of PTX/kg of body weight.

In vivo studies
The mice received one daily IV injection of PTX-LNC or TAXOL® at 12 mg/kg, IV: Q1Dx5 for 5 consecutive days from D0 to D4 (Q1Dx5). The daily treatments are indicated by arrows. Each point represents the mean of the recorded body weight per group (n=12).

Results

Determination of PTX concentration in plasma, tumor, liver, spleen and kidneys originating from BALB/C nude mice bearing subcutaneous SK-OV-3 tumors. The mice received a single IV injection of PTX-LNC or TAXOL® at 20 mg eq PTX/kg. The points represent the individual PTX concentration of each mouse.

Particles characteristics
Mean diameter PTX-LNC: 55 nm (Intensity); Pdl ≤ 0.08
Potential: -12.2 mV
Encapsulation efficiency after DSPE-PEG 2000 insertion: 87 %
pH = 7.4

Mean tumor volume curves
Mean tumor volume curves of BALB/C nude mice bearing subcutaneous SK-OV-3 tumors. The mice received one daily IV injection of PTX-LNC or TAXOL® for 5 consecutive days from D0 to D4 (Q1Dx5). The daily treatments are indicated by arrows. Each point represents the mean of the recorded body weight per group (n=12).

Conclusions

Despite transient BW losses, PTX-LNC was well tolerated by BALB/C nude mice bearing subcutaneous SK-OV-3 tumors.

Based upon the evaluation criteria of antitumor activity, a marked inhibition of the tumor growth was observed for mice treated with PTX-LNC and TAXOL® when compared to mice treated with NaCl 0.9 %.

A marked and significant decrease of the mean tumor volume at D28 was observed for mice treated with PTX-LNC and TAXOL® when compared to mice treated with NaCl 0.9 %.

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