Pharmacokinetics of Nano versus Conventional Formulations of A83B4C63, a Novel Inhibitor of DNA Repair in Rat

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Purpose: There is an increasing interest in the development of DNA repair inhibitors in order to increase the efficacy of radiation and conventional chemotherapy in cancer treatment. However, in order to avoid reducing the repair capacity of normal tissue, it is highly desirable to target the DNA repair inhibitors to tumor. The long term aim of this study is to develop nanodelivery systems for the encapsulation and tumor targeted delivery of A83B4C63, a novel imidopiperidine-based inhibitor of the DNA 3'-phosphatase activity of polynucleotide kinase/phosphatase (PNKP), which is known to play a critical role in rejoining DNA single- and double-strand breaks. Here, A83B4C63 was encapsulated in polymeric micelles of poly(ethylene oxide)-b-poly(e-caprolactone) (PEO-b-PCL) and PEO-poly(α-benzyl carboxylate-e-caprolactone) (PEO-b-PBCL) with degree of polymerization of 44 and 26 in their hydrophobic block, respectively. The Pharmacokinetics of A83B4C63 as part of these nano-formulations was then compared to that of conventional water solubilized formulations of this drug in healthy rats.

Method: PEO-b-PCL and PEO-b-PBCL copolymer were synthesized by ring-opening polymerization and used to form micelles encapsulating A83B4C63. Micellar size and polydispersity index (PDI) were determined using Zetasizer Nano ZS. The release of A83B4C63 from Cremophor/ethanol (Control), PEG 400, PEO-b-PCL and PEO-b-PBCL formulations were assessed using 4% Bovine Serum Albumin (BSA) as recipient phase. Single 10 mg/kg i.v. dose of polymeric micellar and Cremophor/ethanol formulations of A83B4C63 and also A83B4C63 dissolved in PEG 400 were administered to cannulated male Sprague-Dawley rats (n=4/group; Weight: 260 ± 10g). Serial blood samples (200 μL) were collected prior and up to 72 h post-dose and plasma A83B4C63 concentrations were determined using LC/MS/MS. Pharmacokinetic parameters were calculated using a non-compartmental method.

Result: The A83B4C63 was rapidly released from Cremophor/ethanol formulation (63.18±0.56% release in 24 h) and PEG 400 (92.17±0.41% release in 24h). In comparison, both polymeric micellar formulations showed a significant ability to retain the drug after 24 h (P8CL: 25.31±11.80, PCL: 17.64±6.85 % drug release at 24 h). No significant differences were observed in the release pattern between the two polymeric micellar formulations. Our pharmacokinetic results indicating both micellar formulations produced significantly longer MRT and \( t_{1/2} \) when compared to Cremophor/ethanol and PEG formulations.