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Abstract LB-165: Safety and pharmacokinetics of liposomal curcumin in healthy subjects:A randomized placebo-controlled double blind first-in human study.

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Abstract

Purpose: Curcumin exerts anti-proliferative and pro-apoptotic effects against various tumors in vitro and in vivo, and it has been found to suppress carcinogenesis in various organs. A liposomal curcumin formulation was developed enabling intravenous application.

Methods: 50 healthy male or female subjects between 18 and 45 years were allocated to receive single ascending doses of liposomal curcumin as a continuous infusion over 120 min. Dose levels ranged from 10 to 400 mg/m^2. Within each dose group one subject was randomized to receive placebo. A premedication of intravenous diphenhydramine and dexamethasone or diphenhydramine alone was administered to prevent hypersensitivity reactions. Pharmacokinetic assessments included plasma and urine levels of Curcumin and tetrahydrocurcumin (THC), the active metabolite of Curcumin and were analyzed by a validated LC/MS/MS method. Safety assessments included monitoring for adverse events, laboratory safety parameters with special focus on hemolysis, vital signs and ECG.

Results and Conclusions: Liposomal curcumin infusions were tolerated without clinical symptoms. At the maximum tolerated dose of 400 mg/m2 of liposomal curcumin, transient increases in erythrocyte mean cell volume, echinocyte formation, and increased plasma lactate were observed. Markers of hemolysis (HBDH, potassium, haptoglobin, LDH, erythrocytes, Hb) did not change significantly, however, a tendency of erythrocyte loss (-0.5 T/l) was observed.

At a dose of 120 mg/m^2 intermittent echinocyte formation of some erythrocytes was evident. Curcumin and THC levels were established rapidly forming a plateau during infusion with Cmax for curcumin ranging between 42 ± 22 and 2359 ± 412 ng/mL for doses of 10 to 400mg/m^2, respectively. Cmax for THC was 7.1 - 15.8-fold lower than Cmax of curcumin. Upon termination of infusion Curcumin and THC were rapidly cleared from plasma with a mean residence time of 0.62 hr for curcumin and 1.69 hr for THC. Urinary curcumin levels accounted for <0.12% of total systemic clearance.Conclusions: Relevant plasma levels of Curcumin were achieved by infusion of liposomal curcumin over 120 min. A continuous infusion (eg 24h) seems appropriate to achieve sustained exposure to curcumin. 120 mg liposomal curcumin/m^2 is proposed as safe starting dose for phase I studies in patients with solid tumors.

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