

Answer 1:

Bibliographic Information

Plasma, tumor, and tissue disposition of STEALTH liposomal CKD-602 (S-CKD602) and nonliposomal CKD-602 in mice bearing A375 human melanoma xenografts. Zamboni, William C.; Strychor, Sandra; Joseph, Erin; Walsh, Dustin R.; Zamboni, Beth A.; Parise, Robert A.; Tonda, Margaret E.; Yu, Ning Y.; Engbers, Charles; Eiseman, Julie L. Department of Pharmaceutical Sciences, School of Pharmacy, Division of Hematology/Oncology, Department of Medicine, School of Medicine, Molecular Therapeutics Drug Discovery Program, University of Pittsburgh, Pittsburgh, PA, USA. *Clinical Cancer Research* (2007), 13(23), 7217-7223. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 148:479336 AN 2007:1381660 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

S-CKD602 is a STEALTH liposomal formulation of CKD-602, a camptothecin analog. The cytotoxicity of camptothecin analogs is related to the duration of exposure in the tumor. STEALTH liposomal formulations contain lipid conjugated to methoxypolyethylene glycol and have been designed to prolong drug circulation time, increase tumor delivery, and improve the therapeutic index. For STEALTH liposomal formulations of anticancer agents to achieve antitumor effects, the active drug must be released into the tumor extracellular fluid (ECF). S-CKD602 at 1 mg/kg or nonliposomal CKD-602 at 30 mg/kg was administered once via tail vein to mice bearing A375 human melanoma xenografts. Mice (n = 3 per time point) were euthanized at 0.083 to 24 h, 48 h, and 72 h after S-CKD602 and from 0.083 to 24 h after nonliposomal CKD-602. Plasma samples were processed to measure encapsulated, released, and sum total (encapsulated plus released) CKD-602, and tumor and tissue samples were processed to measure sum total CKD-602. Microdialysis samples of tumor ECF were obtained from 0 to 2 h, 4 to 7 h, and 20 to 24 h after nonliposomal CKD-602 and from 0 to 2 h, 24 to 27 h, 48 to 51 h, and 72 to 75 h after S-CKD602. A liq. chromatog.-mass spectrometry assay was used to measure the total (sum of lactone and hydroxyl acid) CKD-602. The area under the concn.-vs.-time curves (AUC) from 0 to infinity and time >1 ng/mL in tumor were estd. For S-CKD602, the CKD-602 sum total AUC in plasma and tumor and the CKD-602 AUC in tumor ECF were 201,929, 13,194, and 187 ng/mL h, resp. For S-CKD602, 82% of CKD-602 remains encapsulated in plasma. For nonliposomal CKD-602, the CKD-602 AUC in plasma and tumor and the CKD-602 AUC in tumor ECF were 9117, 11,661, and 639 ng/mL/h, resp. The duration of time the CKD-602 concn. was >1 ng/mL in tumor ECF after S-CKD602 and nonliposomal CKD-602 was >72 and .apprx.20 h, resp. For S-CKD602, the CKD-602 sum total exposure was 1.3-fold higher in fat as compared with muscle. The ratio of CKD-602 sum total exposure in fat to muscle was 3.8-fold higher after administration of S-CKD602 compared with nonliposomal CKD-602. S-CKD602 provides pharmacokinetic advantages in plasma, tumor, and tumor ECF compared with nonliposomal CKD-602 at 1/30th of the dose, which is consistent with the improved antitumor efficacy of S-CKD602 in preclin. studies. The distribution of S-CKD602 is greater in fat compared with muscle whereas the distribution of nonliposomal CKD-602 is greater in muscle compared with fat. These results suggest that the body compn. of a patient may affect the disposition of S-CKD602 and released CKD-602.

Answer 2:

Bibliographic Information

STEALTH liposomal CKD-602, a topoisomerase I inhibitor, improves the therapeutic index in human tumor xenograft models. Yu, Ning Y.; Conway, Colleen; Pena, Rhoneil L. S.; Chen, Joy Y. ALZA Corporation, Mountain View, CA, USA. *Anticancer Research* (2007), 27(4B), 2541-2545. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 147:439718 AN 2007:994224 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: CKD-602, a topoisomerase I inhibitor, has antitumor activity in a broad spectrum of tumor types. STEALTH liposomal CKD-602 (S-CKD602) prolongs circulation of CKD-602 in plasma, increases drug exposure in tumors and improves efficacy compared with free drug. Materials and Methods: Different dosing regimens of S-CKD602, free CKD-602 and topotecan were compared for antitumor activity in female athymic nude mice bearing human A375 melanoma, ES-2 ovarian, H82 SCLC or HT-29 colon tumor xenografts. Results: S-CKD602 was more efficacious than free drug in all tumor types studied. The therapeutic index (TI) of

S-CKD602 was estd. to be .apprx.6-fold greater than that of free CKD-602 in ES-2 and .apprx.3-fold greater in H82 tumors. TI of S-CKD602 was .apprx.2-fold greater than that of free CKD-602 and .apprx.5-fold greater than that of topotecan in A375, and ≥ 3 -fold greater in HT-29 tumors. In A375 tumors, once-weekly dosing of S-CKD602 was superior to once every 2 wk or twice weekly schedules. Conclusion: The therapeutic index of S-CKD602 was greater than that of free CKD-602 and topotecan in several human tumor types.