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Potent antitumor effect of SN-38-incorporating polymeric micelle, NK012, against malignant glioma.

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Recent published reports on clinical trials of CPT-11 indicate the effectiveness of this compound, a prodrug of SN-38, against malignant glioma in combination with anti-vascular endothelial growth factor antibody. Here, we determined if NK012, and SN-38 incorporating micelle, can be an appropriate formulation for glioblastoma treatment compared with CPT-11. In vitro cytotoxicity was evaluated against several glioma lines with NK012, CPT-11, SN-38, ACNU, CDDP and etoposide. For the in vivo test, a human glioma line (U87MG) transfected with the luciferase gene was inoculated into nude mice brain for pharmacokinetic analysis by fluorescence microscopy and high-performance liquid chromatography after intravenous injection of NK012 and CPT-11. In vivo antitumor activity of NK012 and CPT-11 was evaluated by bioluminescence image and Kaplan-Meier analyses. The growth-inhibitory effects of NK012 were 34- to 444-fold more potent than those of CPT-11. Markedly enhanced and prolonged distribution of free SN-38 in the xenografts was observed after NK012 injection compared with CPT-11. NK012 showed significantly potent antitumor activity against an orthotopic glioblastoma multiforme xenograft and significantly longer survival rate than CPT-11 ($p = 0.0014$). This implies that NK012 can pass through the blood brain tumor barrier effectively. NK012, which combines enhanced distribution with prolonged sustained release, may be ideal for glioma treatment. Currently, a phase I study of NK012 is almost complete in Japan and the US. The present translational study warrants the clinical phase II study of NK012 in patients with malignant glioma. (c) 2008 Wiley-Liss, Inc.

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