Enhanced distribution of NK012, a polymeric micelle-encapsulated SN-38, and sustained-release of SN-38 within tumors can beat a hypovascular tumor

( NK012 の腫瘍内集積と SN-38 の長期徐放能が血管の乏しい腫瘍に有効である )

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Human pancreatic cancer is generally hypovascular in nature and rich in interstitium. These pathological barriers may be some of the factor that make human pancreatic cancer intractable, because they may hinder the penetration of anticancer agents throughout the pancreatic tumor tissue. Approximately 80% of the SN-38 inside NK012, a SN-38 incorporating micelles, can be gradually released within under physiological conditions. The aim of this study was to determine if NK012 may be an appropriate formulation for the treatment of hypovascular tumors. Among pancreatic tumor xenografts, PSN1 appeared to have the richest tumor vasculature and the least number of stromal cells and matrix. On the other hand, Capan1 had the poorest tumor vasculature and most abundant stromal tissue. Fluorescence microscopy and HPLC analysis demonstrated that while NK012 accumulated and continued to be distributed for more than 48 hs throughout the entire body of both tumors, CPT-11 disappeared almost entirely from both tumors within 6 hs. In addition, efficient sustained-release of SN-38 was maintained for more than 96 hs in both tumors following administration of NK012. On the other hand, following the administration of CPT-11, SN-38 was no longer detectable after 24 hs in the Capan1 tumor and after 48 hs in the PSN1 tumor. All tumors were eradicated in the mice treated with NK012 but not in those treated with
CPT-11. Since the antitumor activity of SN-38 is time-dependent, NK012, which combines enhanced distribution with sustained release of SN-38 within tumors may be ideal for the treatment of hypovascular tumors, such as pancreatic cancer.

Figure. Anti tumor effect of NK012 and CPT-11.

NK012 (△), CPT-11 (□), or saline (■) was administered i.v. When the mean tumor volumes reached a 300 mm$^3$ (on day 0), NK012 (30 mg/kg/d) or CPT-11 (66.7 mg/kg/d) was administered on days 0, 4, and 8. Each group consisted of 5 mice. A, Capan1 tumor; B, PSN-1 tumor. * $P<0.05$ (NK012 vs CPT-11), ** $P<0.05$ (NK012 vs saline)