Doxorubicin

NK-911

NK-911 was the first polymeric micelle system to enter human clinical trials successfully in Japan. NK-911 is a PEO-*b*-poly(asptaric acid) with covalently linked doxorubicin side groups in the hydrophobic block (PEO-*b*-P(Asp)-DOX). The modified core block copolymer is used to physically entrap large quantities of DOX. Studies revealed that it is the physically entrapped DOX, and not the chemically conjugated DOX, that plays a significant role in the anti-tumor activity of PEO-*b*-P(Asp)-DOX micelles (Yokoyama et al., 1994). Preclinical studies of NK-911 revealed up to a 28.9-fold increase in the plasmal AUC compared with the commercial formulation, and a 3.4- to 7.4-fold increase in tumor AUC and activity in C26-bearing mice (Yokoyama et al., 1998; Nakanishi et al., 2001). Phase I studies of NK-911 against several advanced tumors determined the micelle formulation to be well tolerated, with major side effects being moderate nausea and vomiting. Currently, phase II studies are underway for patients with metastatic pancreatic cancer at an MTD of 50 mg/m^2 (Matsumura, 2004).

SP-1049C

SP-1049C is a Pluronic formulation of doxorubicin, which uses a mixture of two Pluronics that is, L-61 and F-127, to form a mixed micelle physically entrapping DOX. Preclinical studies of SP-1049C showed a 1.2-fold increase in plasma AUC, a 1.2-fold decrease in CL, and a 1.4-fold decrease in V_d in Lewis lung carcinoma–bearing mice, as compared to free DOX. The toxicity profiles were similar for the micelle formulation and the free drug, but biodistribution experiments indicated a 1.6-fold increase in the brain AUC and 1.7-fold increase in the tumor AUC for SP-1049C (Alakahov, 1999). Phase I clinical trials in Canada of SP-1049C found a slower terminal clearance compared with free conventional DOX, but otherwise phamacokinetics were similar. Dose excalation studies determined that the recommended phase II MTD of SP-1049C be 70 mg/m^2, with dose-limiting myelosuppression at 90 mg/m^2. Evidence of activity was observed in some patients with refractory solid tumors (Danson et al., 2004). A phase II study in inoperable esophagus carcinoma observed partial responses at 75 mg/m^2, and the major side effects were haematological, neutropenia, leucopenia, nausea, anorexia, lethargy, neutropaenia, weight loss, vomiting, mucositis, and alopecia. Half of the recipients had to be reduced to 55 mg/m^2 after the first cycle, and there was a significant fall in cardiac function in some patients, measured as left ventricular ejection fraction (Valle et al., 2004).

Paclitaxel

NK-105

NK-105 is the only micellar formulation of paclitaxel (PAX) so far to show improved pharmacokinetics in preclinical trials compared with the commercial Cremophor EL paclitaxel formulation, Taxol. NK-105 is a PEO-*b*-PBLA formulation physically encapsulating PAX. Preclinical trials found the plasma AUC was 90-fold higher for NK-105 compared with free PAX, owing to lower leakage from normal blood vessels and reduced uptake by the RES. The tumor AUC in a colorectal xenograph was 25-fold higher for NK-105. Furthermore, neurotoxicity was significantly less for NK-105 compared with free PAX (Hamaguchi et al., 2005). Phase I trials of NK-105 began in April 2004, and results are pending.

PAXCEED

The PEO-*b*-P(d, l-lactic acid) (PEO-*b*-PDDLA) formulation of PAX, PAXCEED, was reported by Zhang et al. (1996a) to increase the solubility of PAX 5000-fold, encapsulating 25% w/w PAX. However, preclinical studies found PEO-*b*-PDLLA decreased the AUC of PAX 5.5-fold, and PAX was found to rapidly disassociate from the micelle after intravenous administration to rats