

Review Article

Polymeric Micellar Delivery Systems in Oncology

Yasuhiro Matsumura

Investigative Treatment Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

Received September 1, 2008; accepted September 22, 2008; published online November 6, 2008

The purpose of drug delivery systems in cancer chemotherapy is to achieve selective delivery of anti-cancer agents to cancer tissue at an effective concentrations for the appropriate duration of time, so that we may be able to reduce the adverse effects of a drug and simultaneously enhance the anti-tumor effect. Polymeric micelles were expected to increase the accumulation of drugs in tumor tissues utilizing the enhanced permeability and retention effect and to incorporate various kinds of drugs into the inner core by chemical conjugation or physical entrapment with relatively high stability. The size of the micelles can be controlled within the diameter range of 20–100 nm, to ensure that the micelles do not pass through normal vessel walls; therefore, a reduced incidence of the side effects of the drugs may be expected due to the decreased volume of distribution. There are several anti-cancer agent-incorporated micelle carrier systems under clinical evaluation. Phase 1 studies of a cisplatin-incorporated micelle, NC-6004 and an SN-38-incorporated micelle, NK012, are now underway. A Phase 2 study of a paclitaxel-incorporated micelle, NK105, against stomach cancer is also underway.

Key words: DDS – polymer micelles – clinical trial – EPR effect

INTRODUCTION

There are two main concepts in drug delivery system (DDS), active targeting and passive targeting. Active targeting involves monoclonal antibodies or ligands to tumor-related receptors, which can target the tumor by utilizing the specific binding ability between the antibody and antigen or between the ligand and its receptor. However, the application of DDS using monoclonal antibodies is restricted to tumors expressing high levels of related antigens. The passive targeting system can be achieved by the enhanced permeability and retention (EPR) effect (1). The EPR effect is based on the pathophysiological characteristics of solid tumor tissues: hypervascularity, incomplete vascular architecture, secretion of vascular permeability factors stimulating extravasation within cancer tissue and absence of effective lymphatic drainage from tumors, which impedes the efficient clearance of macromolecules accumulated in solid tumor tissues.

Several techniques to use maximally the EPR effect have been developed, e.g. modification of drug structures and

development of drug carriers. Polymeric micelle-based anti-cancer drugs were originally developed by Prof Kataoka et al. (2–4) in the late 1980s or early 1990s. Polymeric micelles were expected to increase the accumulation of drugs in tumor tissues utilizing the EPR effect and to incorporate various kinds of drugs into the inner core by chemical conjugation or physical entrapment with relatively high stability. The size of the micelles can be controlled within the diameter range of 20–100 nm, to ensure that the micelles do not pass through normal vessel walls; therefore, a reduced incidence of the adverse effects of the drugs may be expected.

In this article, polymeric micelle systems for which clinical trials are now underway are reviewed.

NK105, PACLITAXEL-INCORPORATING MICELLAR NANOPARTICLE

BACKGROUND

Paclitaxel (PTX) is one of the most useful anti-cancer agents known for various cancers, including ovarian, breast and lung cancers (5,6). However, PTX has serious adverse effects, e.g. neutropenia and peripheral sensory neuropathy. In addition, anaphylaxis and other severe hypersensitive reactions have

For reprints and all correspondence: Yasuhiro Matsumura, Investigative Treatment Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan. E-mail: yhmatsum@east.ncc.go.jp

been reported to develop in 2–4% of patients receiving the drug even after premedication (P) with anti-allergic agents; these adverse reactions have been attributed to the mixture of Cremophor EL and ethanol which was used to solubilize PTX (7,8). Of the adverse reactions, neutropenia can be prevented or managed effectively by administering a granulocyte colony-stimulating factor. On the other hand, there are no effective therapies to prevent or to reduce nerve damage, which is associated with peripheral neuropathy caused by PTX; therefore, neurotoxicity constitutes a significant dose-limiting toxicity (DLT) of the drug (9,10).

PRECLINICAL STUDY

To construct NK105 micellar nanoparticles (Fig. 1), block copolymers consisting of polyethylene glycol and polyaspartate, the so-called PEG–polyaspartate described previously (2–4,11), were used. PTX was incorporated into polymeric micelles formed by physical entrapment utilizing hydrophobic interactions between PTX and the block copolymer polyaspartate chain (12).

Pharmacokinetic study showed that NK105 exhibited slower clearance from the plasma than PTX. The plasma concentration at 5 min ($C_{5\text{min}}$) and the area under the curve (AUC) of NK105 were 11- to 20-fold and 50- to 86-fold higher for NK105 than that for PTX, respectively. The maximum concentration (C_{max}) and AUC of NK105 in Colon 26 tumors were ~three times and 25 times higher for NK105 than that for PTX, respectively. NK105 continued to accumulate in the tumors until 72 h after injection (12). In *in vivo* anti-tumor activity, BALB/c mice bearing s.c. HT-29 colon cancer tumors showed decreased tumor growth rates after the administration of PTX and NK105. However, NK105 exhibited superior anti-tumor activity as compared with PTX ($P < 0.001$). The anti-tumor activity of NK105 administered at a PTX-equivalent dose of 25 mg/kg was comparable to that obtained after the administration of free PTX 100 mg/kg. Tumor suppression by NK105 increased in a dose-dependent manner. Tumors disappeared after the first dosing to mice treated with NK105 at a PTX-equivalent dose of 100 mg/kg, and all mice remained tumor-free thereafter (Fig. 2). In addition, less weight loss was induced in mice

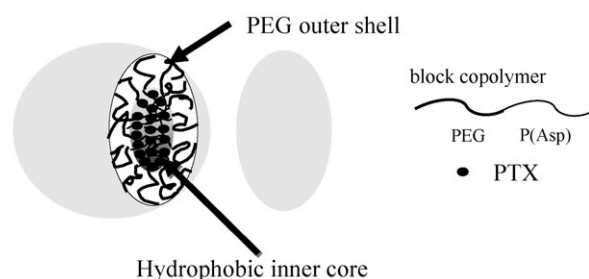


Figure 1. Preparation and characterization of NK105. The micellar structure of NK105 paclitaxel (PTX) was incorporated into the inner core of the micelle. PEG, polyethylene glycol (12).

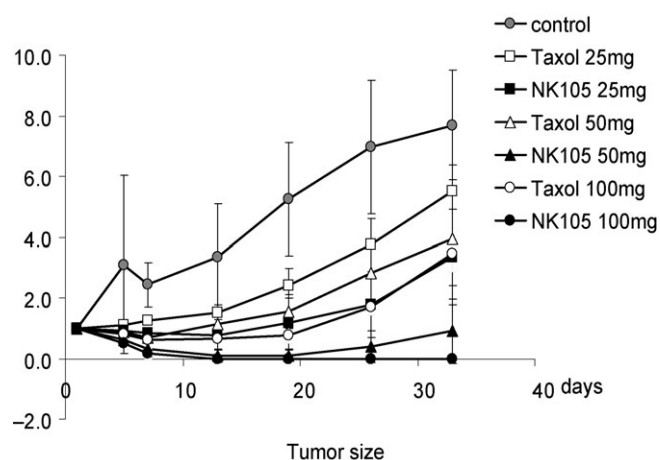


Figure 2. Effects of PTX (open symbols) and NK105 (closed symbols). PTX and NK105 were injected intravenously once weekly for 3 weeks at PTX-equivalent doses of 25 mg/kg (open square, closed square), 50 mg/kg (open triangle, closed triangle) and 100 mg/kg (open circle, closed circle), respectively. Saline was injected to control animals (open square) (12).

given NK105 100 mg/kg than in those given the same dose of free PTX (12).

Treatment with PTX has resulted in cumulative sensory-dominant peripheral neurotoxicity in humans, characterized clinically by numbness and/or paraesthesia of the extremities. Pathologically, axonal swelling, vesicular degeneration and demyelination were observed. We, therefore, examined the effects of free PTX and NK105 using both electrophysiological and morphological methods. Prior to drug administration, there were no significant differences in the amplitude of caudal sensory nerve action potential between two drug administration groups. The amplitude was significantly smaller in the PTX group than in the control group ($P < 0.01$), while the amplitude was significantly larger in the NK105 group than in the PTX group ($P < 0.05$) and was comparable between the NK105 group and the control group (Fig. 3).

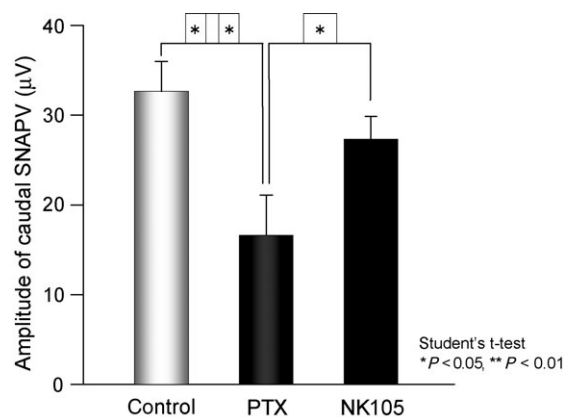


Figure 3. Effects of PTX or NK105 on the amplitude of rat caudal sensory nerve action potentials as examined 5 days after weekly injections for 6 weeks. Rats ($n = 14$) were injected with NK105 or PTX at a PTX-equivalent dose of 7.5 mg/kg. Five percent glucose was also injected in the same manner to animals in the control group (12).

CLINICAL STUDY

A Phase 1 study was designed to determine maximum tolerated dose (MTD), DLTs, the recommended dose (RD) for Phase 2 and the pharmacokinetics of NK105 (13). NK105 was administered by 1-h intravenous infusion every 3 weeks without anti-allergic P. The starting dose was 10 mg PTX-equivalent/m², and dose escalated according to the accelerated titration method. Nineteen patients were treated at the following doses: 10 (*n* = 1), 20 (*n* = 1), 40 (*n* = 1), 80 (*n* = 1), 110 (*n* = 3), 150 (*n* = 7) and 180 mg/m² (*n* = 5). Tumor types treated have included: pancreatic (*n* = 11), bile duct (*n* = 5), gastric (*n* = 2) and colon (*n* = 1). Neutropenia has been the predominant hematological toxicity and Grade 3 or 4 neutropenia was observed in patients treated at 110, 150 and 180 mg/m². One patient at 180 mg/m² developed Grade 3 fever. No other Grade 3 or 4 non-hematological toxicity including neuropathies was observed. DLTs were observed in two patients at the 180 mg/m² (Grade 4 neutropenia lasting for more than 5 days), which was determined as MTD. Allergic reactions were not observed in any of the patients except in one patient at 180 mg/m². A partial response was observed in one pancreatic cancer patient, who received more than 12 courses of NK105 (13) (Fig. 4). Despite the long-time usage, only Grade 1 or 2 neuropathy was observed by modifying the dose or period of drug administration. Colon and gastric cancer patients experienced stable disease lasting 10 and 7 courses, respectively. The *C*_{max} and AUC of NK105 showed dose-dependent

characteristics. The plasma AUC of NK105 at 180 mg/m² was ~30-fold higher than that of the commonly used PTX formulation (13) (Fig. 5). DLT was Grade 4 neutropenia. NK105 generates prolonged systemic exposure to PTX in plasma. Tri-weekly 1-h infusion of NK105 was feasible and well tolerated, with anti-tumor activity in pancreatic cancer patients. A Phase 2 study of NK105 is now underway against advanced stomach cancer as a second line therapy.

NC-6004, CISPLATIN-INCORPORATING MICELLAR NANOPARTICLE

BACKGROUND

Cisplatin [*cis*-dichlorodiammineplatinum (II): CDDP] is a key drug in the chemotherapy for cancers, including lung, gastrointestinal and genitourinary cancer (14,15). However, we often find that it is necessary to discontinue treatment with CDDP due to its adverse reactions, e.g. nephrotoxicity and neurotoxicity, despite its persisting effects (16). Platinum analogues, e.g. carboplatin and oxaliplatin (17), have been developed to date to overcome these CDDP-related disadvantages. Consequently, these analogues are becoming the standard drugs for ovarian (18) and colon cancers (19). However, those regimens including CDDP are considered to constitute the standard treatment for lung, stomach, testicular (20) and urothelial cancers (21). Therefore, the development of a DDS technology is anticipated, which would offer the better selective accumulation

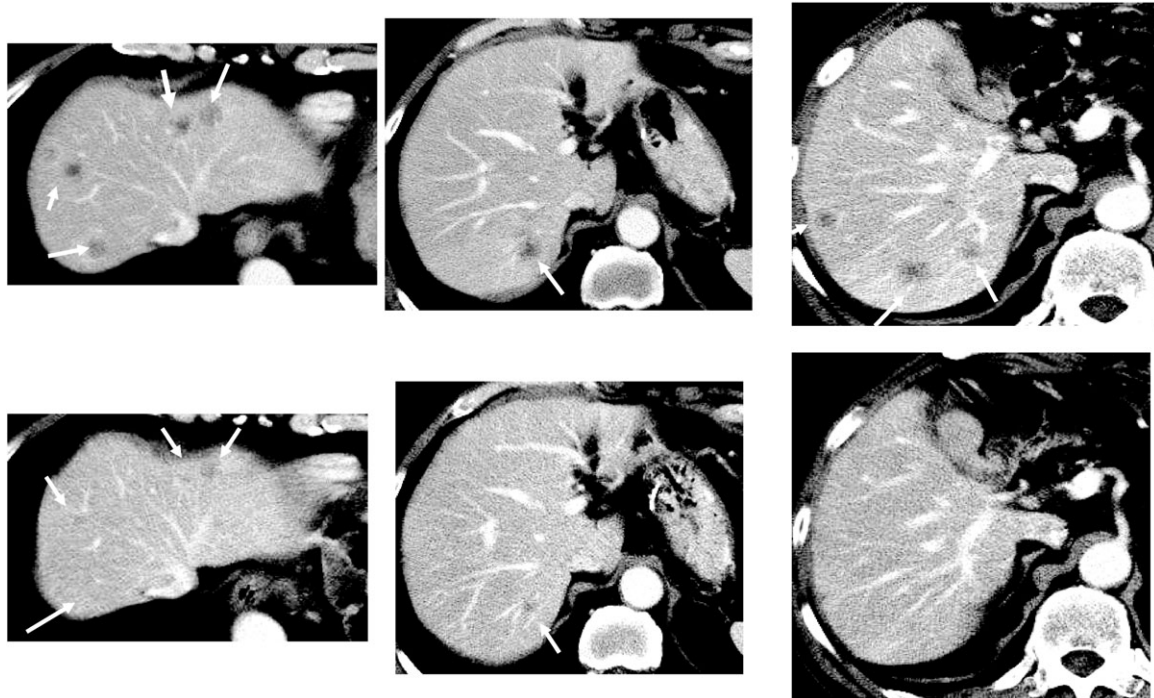


Figure 4. Serial computed tomography (CT) scans. A 60-year-old male with pancreatic cancer, who was treated with NK105 at a dose level of 150 mg/m². Baseline scan (upper panels) showing multiple metastasis in the liver. Partial response, characterized by a more than 90% decrease in the size of the liver metastasis (lower panels) compared with the baseline scan. The anti-tumor response was maintained for nearly 1 year (13).

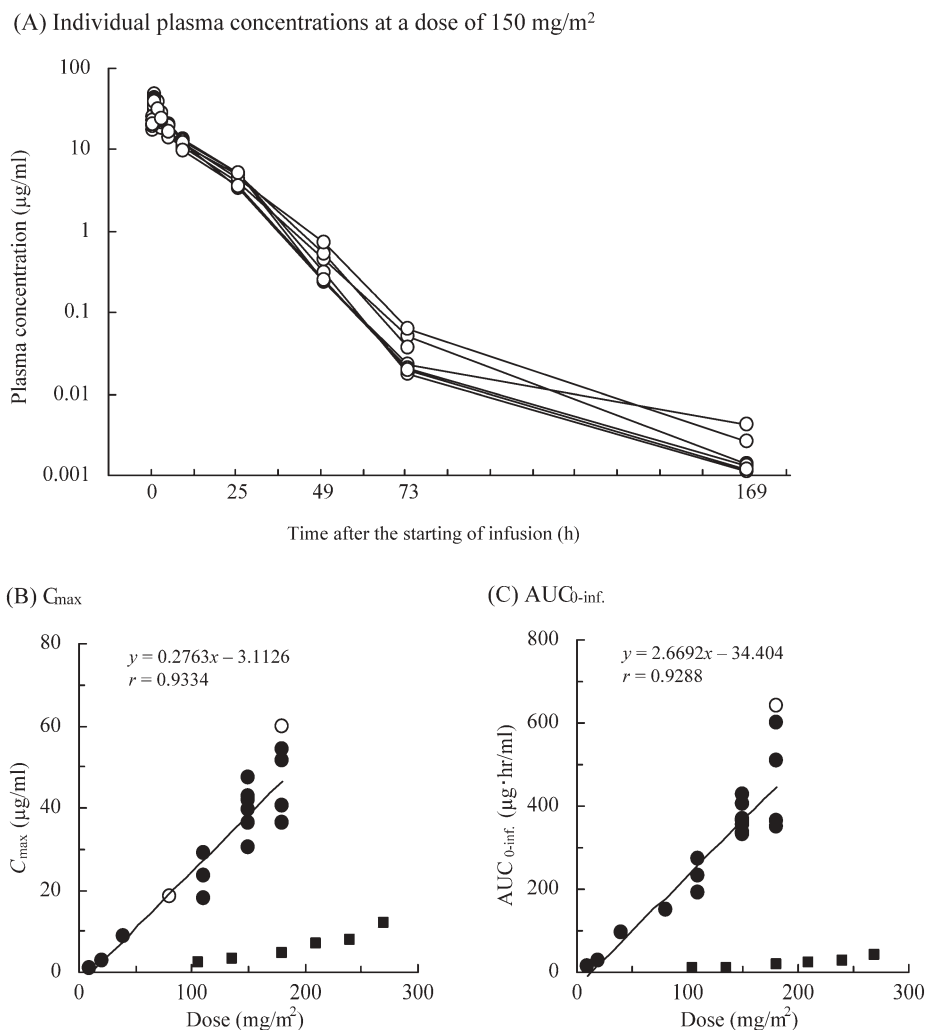


Figure 5. (A) Individual plasma concentrations of PTX in seven patients following 1 h intravenous infusion of NK105 at a dose of 150 mg/m². Relationships between dose and C_{max} (B), and between dose and AUC_{0-inf.} (C) of PTX in patients following 1 h intravenous infusion of NK105. Regression analysis for dose versus C_{max} was applied using all points except for one patient at 80 mg/m² whose medication time became 11 min longer and one patient at 180 mg/m² who had medication discontinuation and steroid medication (open circle). Regression analysis for dose vs. AUC_{0-inf.} was applied using all points except for one patient who had medication discontinuation and steroid medication (closed circle). Relationships between dose and C_{max}, and AUC_{0-inf.} in patients following conventional PTX administration were plotted (closed square) (13).

of CDDP into solid tumors while lessening its distribution into normal tissue.

PRECLINICAL STUDY

NC-6004 consists of PEG, a hydrophilic chain that constitutes the outer shell of the micelles, and the coordinate complex of poly(glutamic acid) [P(Glu)] and CDDP, a polymer–metal complex-forming chain that constitutes the inner core of the micelles (22) (Fig. 6). The molecular weight of PEG-P(Glu) as a sodium salt was ~18 000 [PEG: 12 000; P(Glu): 6000]. The release rates of CDDP from NC-6004 were 19.6 and 47.8% at 24 and 96 h, respectively. In distilled water, furthermore, NC-6004 was stable without releasing cisplatin.

The AUC_{0-t} and C_{max} values were significantly higher in animals given NC-6004 than in animals given CDDP,

namely, 65- and 8-fold, respectively ($P < 0.001$ and 0.001, respectively) (23). The C_{max} in tumor was 2.5-fold higher for NC-6004 than for CDDP ($P < 0.001$). Furthermore, the tumor AUC was 3.6-fold higher for NC-6004 than for CDDP (81.2 and 22.6 µg/ml h in animals given NC-6004 and CDDP, respectively) (23).

BALB/c nude mice implanted with a human gastric cancer cell line MKN-45 showed decreased tumor growth rates after i.v. injection of CDDP and NC-6004 (Fig. 7A). The NC-6004 administration groups at the same dose levels as CDDP showed no significant difference in tumor growth rate. Regarding time-course changes in body weight change rate, the CDDP 5 mg/kg administration group showed a significant decrease ($P < 0.001$) in body weight as compared with the control group. On the other hand, NC-6004 administration group did not show a decrease in body weight as compared with the control group (Fig. 7B).

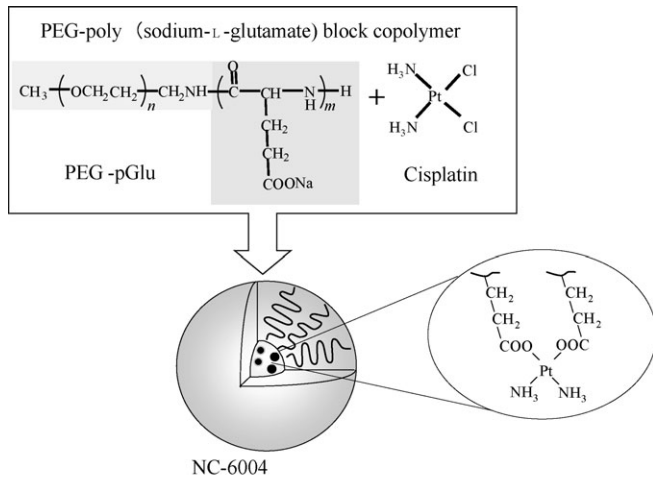


Figure 6. Preparation and characterization of cisplatin (CDDP)-incorporating polymeric micelles (NC-6004). Chemical structures of CDDP and polyethylene glycol poly(glutamic acid) block copolymers [PEG-P(Glu) block copolymers], and the micellar structures of CDDP-incorporating polymeric micelles (NC-6004) (22).

Regarding toxicity, the CDDP 10 mg/kg administration group showed significantly higher plasma concentrations of blood urea nitrogen and creatinine as compared with the control group ($P < 0.05$ and 0.001 , respectively), with the NC-6004 10 mg/kg administration group ($P < 0.05$ and 0.001 , respectively) (Fig. 8A and B). Light microscopy indicated tubular dilation with flattening of the lining cells of the tubular epithelium in the kidney from all animals in the CDDP 10 mg/kg administration group. On the other hand, no histopathologic change was observed in the kidneys from all animals in the NC-6004 10 mg/kg administration group (data not shown). Animals given NC-6004 showed no delay in sensory nerve condition velocities (SNCVs) as compared with animals given 5% glucose. On the other hand, animals given CDDP showed a significant delay ($P < 0.05$) in SNCV

as compared with animals given NC-6004 (Fig. 9A). The analysis by ICP-MS on sciatic nerve concentrations of platinum showed that the concentrations were significantly ($P < 0.05$) lower in animals given NC-6004 (Fig. 9B). This finding is believed to be a factor that reduced neurotoxicity following NC-6004 administration as compared with the CDDP administration (23).

CLINICAL STUDY

A Phase 1 trial was run in two UK experimental cancer medicine centers with the PK assays performed in a good laboratory practice-accredited laboratory in Newcastle University (24).

Patients with solid tumors were included in this open-label trial. Usual Phase 1 inclusion and exclusion criteria were applied, including adequate renal function. Patients were limited to one previous course of platinum-based treatment with maximum dose limits of cisplatin, carboplatin or oxalipatin.

Dose escalation proceeded in two stages. In Stage 1, we recruited cohorts of one to three patients until Grade 2 toxicity was seen in Cycle 1. In Stage 2, we had cohorts of three patients expanding to six if one of three DLT and to confirm MTD.

The starting dose for the Phase 1 study was 10 mg/m². NC-6004 was administered as a 60 min infusion with a total infusion volume of 500 ml. Treatment was repeated on a 3-weekly cycle until progressive disease, intolerance of the agent or patient withdrawal. Pharmacokinetic analysis of total plasma platinum (Pt), micellar Pt and ultrafiltrate Pt (UF Pt) was performed using WinNonlin version 1.3 to calculate C_{max} , T_{max} , half-life and AUC for all Pt species. Clearance and volume of distribution were calculated based on the measurements of total and micellar Pt.

In this trial, 17 patients (10 male, 7 female) were treated. The median age (range) was 59 years (40–80), and tumor

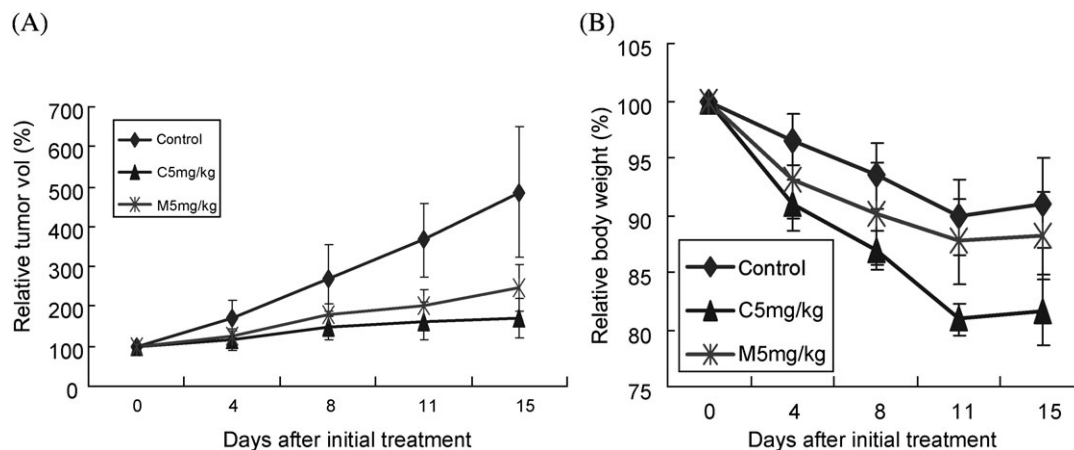


Figure 7. Relative changes in MKN-45 tumor growth rates in nude mice. (A) CDDP (closed triangle) and NC-6004 (cross symbol) were injected intravenously every 3 days, three administrations in total, at CDDP-equivalent doses of 5 mg/kg. Five percent glucose was injected in the control mice (open diamond). (B) Changes in relative body weight. Data were derived from the same mice as those used in the present study. Values are expressed as the mean \pm SE (23).

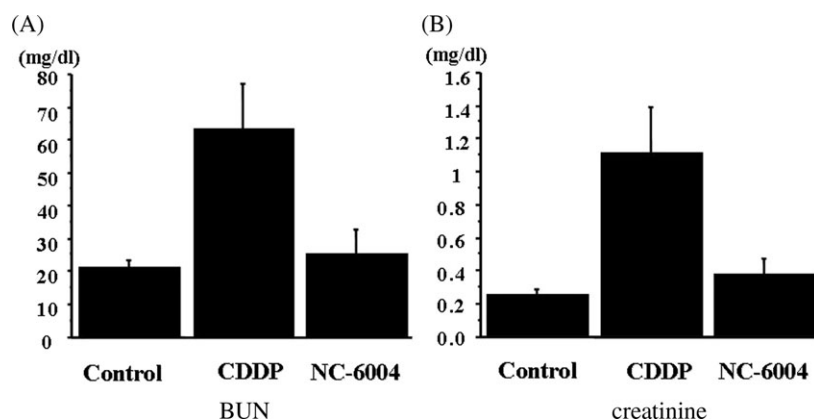


Figure 8. Nephrotoxicity of CDDP and NC-6004. Plasma concentrations of blood urea nitrogen (BUN) and creatinine were measured after a single i.v. injection of 5% glucose ($n = 8$), CDDP at a dose of 10 mg/kg ($n = 12$), NC-6004 at a dose of 10 mg/kg ($n = 13$) on a CDDP basis (23).

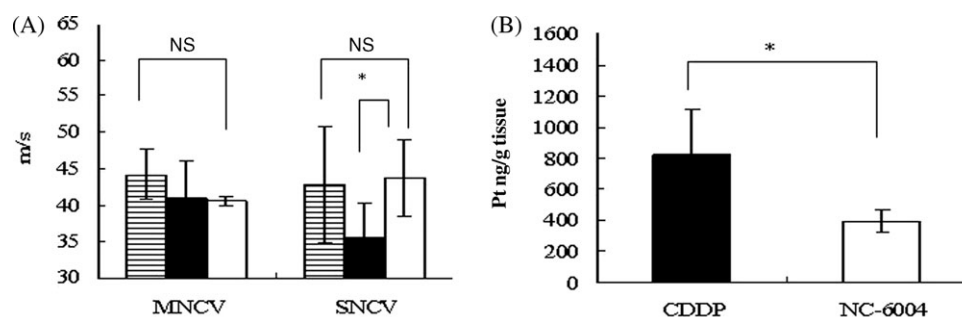


Figure 9. Neurotoxicity of CDDP and NC-6004 in rats. Rats ($n = 5$) were given CDDP (2 mg/kg), NC-6004 (an equivalent dose of 2 mg/kg CDDP), or 5% glucose, all intravenously twice a week, 11 administrations in total. Sensory nerve conduction velocity and motor nerve conduction velocity of the sciatic nerve at Week 6 after the initial administration (A). The platinum concentration in the sciatic nerve. Rats were given CDDP (5 mg/kg, $n = 5$), NC-6004 (an equivalent dose of 5 mg/kg CDDP, $n = 5$) or 5% glucose ($n = 2$), all intravenously twice a week, four administrations in total. On Day 3 after the final administration, a segment of the sciatic nerve was removed and the platinum concentration in the sciatic nerve was measured by ICP-MS (B). The data are expressed as the mean \pm SD. * $P < 0.05$ (23).

types included colorectal (4), NSCLC (3), esophageal (2), pancreatic (2), melanoma (2) and one each of GIST, mesothelioma, renal cell and hepatocellular cancer. Treatment was well tolerated with little nausea (no routine use of prophylactic antiemetics) and no protocol-defined DLTs were observed. There was no myelotoxicity or neurotoxicity and no changes in audiometry (Table 1).

A Grade 2 fall in ethylenediamine tetraacetic acid (EDTA) glomerular filtration rate (GFR) was observed at 40 mg/m², and post-hydration (H) with 1L N saline IV over 30 min for all patients was therefore instituted and followed by administration of doses up to 120 mg/m² without significant nephrotoxicity. Four hypersensitivity reactions occurred in the first nine patients on or after Cycle 2. After introduction of P with anti-histamines and corticosteroids, two further reactions were seen, during the third or fourth cycle. Three patients had previous platinum exposure, and three were platinum-naïve (Table 1).

The best response was stable disease and this was seen in seven of 17 (41%) patients.

In the ultrafiltrate fraction, there was delayed ($T_{\max} = 24$ h) and prolonged (half-life 68–580 h) detection of small

molecular weight platinum species. NC-6004 provides a sustained release of potentially active platinum species. Using gel-filtration, we have been able to separate the Pt present in the original formulation from other Pt species in the plasma. The kinetics of UF Pt indicated a delayed and sustained release of cisplatin after dosing with NC-6004.

This novel formulation of cisplatin is well tolerated with minimal nephrotoxicity and no significant myelosuppression, emesis or neurotoxicity but a higher rate of hypersensitivity reactions than predicted. Disease stabilization has been seen in heavily pre-treated patients with efficacy best assessed in future Phase 2 trials. The recommended Phase 2 dose of NC-6004 for monotherapy is 90–120 mg/m² and for the combination is 60–90 mg/m².

NK012, SN-38-INCORPORATING MICELLAR NANOPARTICLE

BACKGROUND

The anti-tumor plant alkaloid camptothecin (CPT) is a broad-spectrum anti-cancer agent that targets the DNA

Table 1. Patient results of NC-6004 Phase 1 trial

Dose level (mg/m ²)	No of patients	No of cycles (median)	Renal impairment	EDTA GFR change (ml/min)	Hypersensitivity (cycle)	Best response
1 (10)	1	3			Gr 2 (C3)	SD
2 (20)	1	2				PD
3 (40)	3	1–4 (2)	Gr 2 (C1)	95 → 39		1 SD 2 PD
4 (60)	3	2 (2)			Gr 1 (C2)	1 NE
+ H					Gr 3 (C2)	2 PD
5 (90)	6	2–4 (2)	Gr 2 (C1)	74 → 59	Gr 3 (C4)	3 SD
+H			Gr 2 (C2)	67 → 53		3 PD
6 (120)	3	2–4 (3)			Gr 2 (C4)	2 SD
+ H + P					Gr 3 (C3)	1 PD

A Grade 2 fall in EDTA GFR was observed at 40 mg/m² and hydration with 1000 ml saline i.v. over 30 mm for all patients was therefore instituted and following this administration of doses up to 120 mg/m² without significant nephrotoxicity was performed (24). EDTA, ethylenediamine tetraacetic acid; GFR, glomerular filtration rate; Gr, grade; C, cycle; SD, standard deviation; PD, progressive disease; NE, not evaluated.

topoisomerase I. Although CPT has showed promising anti-tumor activity *in vitro* and *in vivo* (25,26), it has not been used clinically because of its low therapeutic efficacy and severe toxicity (27,28). Among CPT analogs, irinotecan hydrochloride (CPT-11) has recently been demonstrated to be active against colorectal, lung and ovarian cancers (29–33). CPT-11 itself is a prodrug and is converted to 7-ethyl-10-hydroxy-CPT (SN-38), a biologically active metabolite of CPT-11, by carboxylesterases (CEs). SN-38 exhibits up to 1000-fold more potent cytotoxic activity against various cancer cells *in vitro* than CPT-11 (34). Although CPT-11 is converted to SN-38 in the liver and tumor, the metabolic conversion rate is <10% of the original volume of CPT-11 (35,36). In addition, the conversion of CPT-11 to SN-38 depends on the genetic inter-individual variability of CE activity (37). Thus, the direct use of SN-38 might be of great advantage, and attractive, for cancer treatment. For the clinical use of SN-38, however, it is essential to develop a soluble form of water-insoluble SN-38. The progress of the manufacturing technology of ‘micellar nanoparticles’ may make it possible to utilize SN-38 for *in vivo* experiments and further clinical use.

PRECLINICAL STUDY

SN-38 was bound to the carboxylic acid on a polyglutamate (PGlu) chain of block copolymer through the ester bond. NK012 is an SN-38-loaded polymeric micelle constructed in an aqueous milieu by the self-assembly of an amphiphilic block copolymer, PEG–PGlu(SN-38) (38) (Fig. 10). The mean particle size of NK012 is 20 nm in diameter with a relatively narrow range. The releasing rates of SN-38 from NK012 in phosphate-buffered saline at 37°C were 57 and 74% at 24 and 48 h, respectively, and that in 5% glucose solution at 37°C were 1 and 3% at 24 and 48 h, respectively. These results indicate that NK012 can release SN-38 under

neutral conditions even without the presence of a hydrolytic enzyme and is stable in 5% glucose solution. It is suggested that NK012 is stable before administration and starts to release SN-38, the active component, under physiological conditions after administration.

In PK study, after injection of CPT-11, the concentrations of CPT-11 and SN-38 for plasma declined rapidly with time in a log-linear fashion. On the other hand, NK012 (polymer-bound SN-38) exhibited slower clearance. The clearance of NK012 in the HT-29 tumor was significantly slower and the concentration of free SN-38 was maintained at >30 ng/g even at 168 h after injection. Anti-tumor activity of NK012 was evaluated in lung (38), renal (39), pancreatic (40) and stomach cancers xenografts (41) in comparison with CPT-11. NK012 exhibited superior anti-tumor activity in all tumors tested compared with CPT-11. Also, the therapeutic effect of NK012/5FU was significantly superior to that of CPT-11/5FU against the HT-29 xenografts ($P = 0.0004$). A 100% CR rate was obtained in the NK012/5FU group, as compared with the 0% CR rate in the CPT-11/5FU (Fig. 11) (42).

It may be concluded that NK012 can selectively accumulate in any tumor xenografts, to be distributed effectively throughout the entire body of the tumor, including in hypovascular tumors, and show sustained-release for a prolonged period of time. Consequently, NK012 can exert more significant anti-tumor activity as compared with CPT-11, which is not an ideal formulation for realizing the time-dependent actions of the drug (40).

CLINICAL STUDY

Two independent Phase 1 studies of NK012 have been almost completed in the National Cancer Center in Japan (43) and the Sarah Canon Cancer Center in the USA (44) in patients with advanced solid tumors to determine the

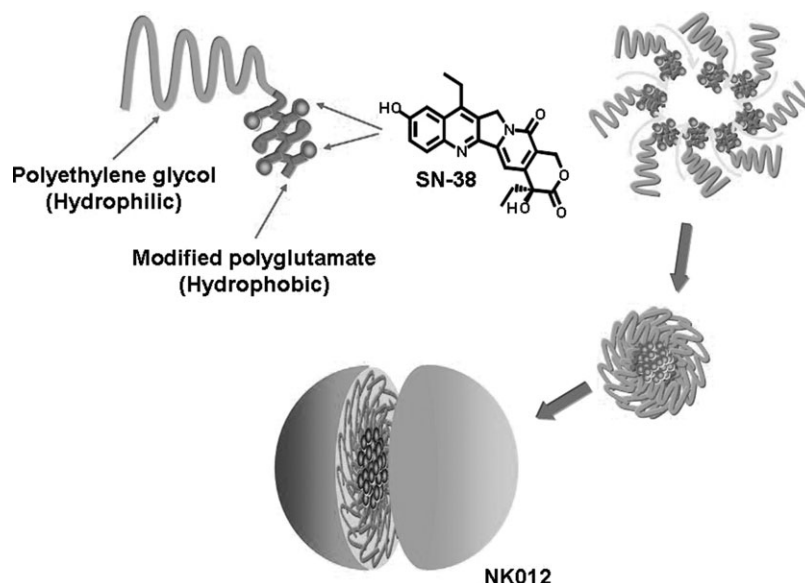


Figure 10. Schematic structure of NK012. A polymeric micelle carrier of NK012 consists of a block copolymer of PEG (molecular weight of ~5000) and partially modified polyglutamate (~20 U). Polyethylene glycol (hydrophilic) is believed to be the outer shell and SN-38 was incorporated into the inner core of the micelle (38).

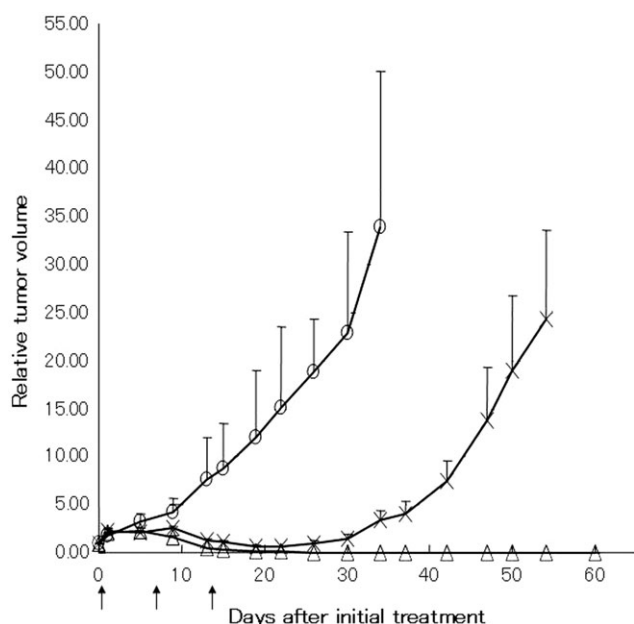


Figure 11. Effect of NK012/5-FU as compared with that of CPT-11/5-FU against HT-29 tumor-bearing mice. (Open circle) control, (cross symbol) CPT-11 50 mg/kg 24 h before 5-FU 50 mg/kg, (closed triangle) NK012 10 mg/kg 24 h before 5-FU 50 mg/kg (42).

pharmacokinetics, toxicity profile and the RD for Phase 2 of NK012. NK012 is infused intravenously over 30 min every 21 days until disease progression or unacceptable toxicity occurs. UGT1A1 genotype screening was performed prior to enrollment, and UGT1A1*28/*28 homozygotes were treated at a reduced dose level with the potential for dose escalation based on toxicities. In a Japanese study, the starting dose was 2 mg/m² as an SN-38 equivalent, and the dose was

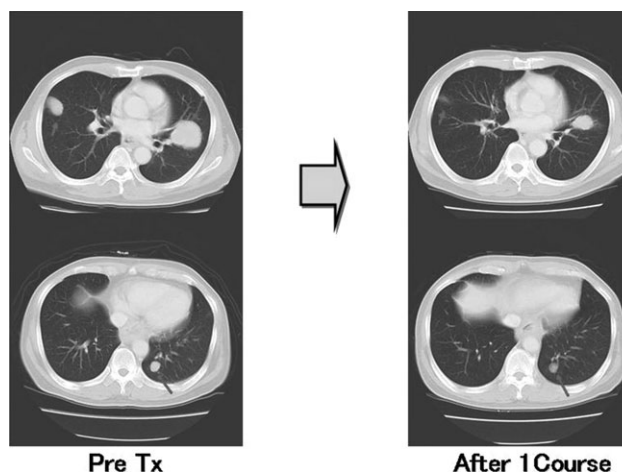


Figure 12. CT scan of an esophageal cancer patient with lung metastasis. This patient had previously undergone 5-FU+CDDP followed by taxotere. Partial response, characterized by a more than 50% decrease in size of the lung metastasis compared with the baseline scan (43).

escalated by the accelerated titration method. In an US study, the starting dose was 9 mg/m² as an SN-38 equivalent and at least three patients were treated at each dose level.

DLT was determined to be neutropenia. MTD will become >28 mg/m² and RD may become ≤28 mg/m². Non-hematological toxicities including diarrhea were mostly less than Grade 2 in Course 1. One partial response has been reported in a patient with esophageal cancer in a Japanese study (Fig. 12), and three patients with triple negative breast cancer and one patient with small cell lung cancer had PR in the US study. In conclusion, NK012 is well tolerated and has demonstrated anti-tumor activity in patients with refractory tumors.

CONCLUSION

A quarter of a century has passed since the EPR effect was discovered. Until recently, the EPR had not been recognized in the field of oncology. However, many oncologists have now become acquainted with it, since some drugs such as doxil, abraxane and several PEGylated proteinaceous agents formulated based on the EPR have been approved in the field of oncology. Micelle carrier systems described in this article are obviously categorized as DDS based on the EPR. It is expected that some anti-cancer agents incorporating micelle nanoparticles may be approved for clinical use soon.

Our next task is to develop DDS, which can accumulate selectively in solid tumors but also allow distribution of the delivered bullets (anti-cancer agents) through the entire mass of the solid tumor tissue.

Funding

This work was supported partly by a Grant-in-Aid from the 3rd Term Comprehensive Control Research for Cancer, Ministry of Health, Labor and Welfare (Y. Matsumura) and Scientific Research on Priority Areas from the Ministry of Education, Culture, Sports, Science and Technology (Y. Matsumura), and the Princess Takamatsu Cancer Research Fund (Y. Matsumura).

Conflict of interest statement

None declared.

References

- Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumorotropic accumulation of proteins and the antitumor agent smancs. *Cancer Res* 1986;46:6387–92.
- Kataoka K, Kwon GS, Yokoyama M, Okano T, Sakurai Y. Block copolymer micelles as vehicles for drug delivery. *J Controlled Release* 1993;24:119–32.
- Yokoyama M, Miyauchi M, Yamada N, Okano T, Sakurai Y, Kataoka K, et al. Polymer micelles as novel drug carrier: adriamycin-conjugated poly(ethylene glycol)-poly(aspartic acid) block copolymer. *J Controlled Release* 1990;11:269–78.
- Yokoyama M, Okano T, Sakurai Y, Ekimoto H, Shibazaki C, Kataoka K. Toxicity and antitumor activity against solid tumors of micelle-forming polymeric anticancer drug and its extremely long circulation in blood. *Cancer Res* 1991;51:3229–36.
- Khayat D, Antoine EC, Coeffic D. Taxol in the management of cancers of the breast and the ovary. *Cancer Invest* 2000;18:242–60.
- Carney DN. Chemotherapy in the management of patients with inoperable non-small cell lung cancer. *Semin Oncol* 1996;23:71–5.
- Weiss RB, Donehower RC, Wiernik PH, Ohnuma T, Gralla RJ, Trump DL, et al. Hypersensitivity reactions from taxol. *J Clin Oncol* 1990;8:1263–8.
- Rowinsky EK, Donehower RC. Paclitaxel (taxol). *N Engl J Med* 1995;332:1004–14.
- Rowinsky EK, Chaudhry V, Forastiere AA, Sartorius SE, Ettinger DS, Grochow LB, et al. Phase I and pharmacologic study of paclitaxel and cisplatin with granulocyte colony-stimulating factor: neuromuscular toxicity is dose-limiting. *J Clin Oncol* 1993;11:2010–20.
- Wasserheit C, Frazein A, Oratz R, Sorich J, Downey A, Hochster H, et al. Phase II trial of paclitaxel and cisplatin in women with advanced breast cancer: an active regimen with limiting neurotoxicity. *J Clin Oncol* 1996;14:1993–9.
- Yokoyama M, Okano T, Sakurai Y, Ekimoto H, Shibazaki C, Kataoka K. Toxicity and antitumor activity against solid tumors of micelle-forming polymeric anticancer drug and its extremely long circulation in blood. *Cancer Res* 1991;51:3229–36.
- Hamaguchi T, Matsumura Y, Suzuki M, Shimizu K, Goda R, Nakamura I, et al. NK105, a paclitaxel-incorporating micellar nanoparticle formulation, can extend in vivo antitumor activity and reduce the neurotoxicity of paclitaxel. *Brit J Cancer* 2005;92:1240–6.
- Hamaguchi T, Kato K, Yasui H, Morizane C, Ikeda M, Ueno H, et al. A Phase I and Pharmacokinetic Study of NK105, a paclitaxel-incorporating micellar nanoparticle formulation. *Brit J Cancer* 2007;97:170–6.
- Horwich A, Sleijfer DT, Fossa SD, Kaye SB, Oliver RT, Cullen MH, et al. Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. *J Clin Oncol* 1997;15:1844–52.
- Roth BJ. Chemotherapy for advanced bladder cancer. *Semin Oncol* 1996;23:633–44.
- Pinzani V, Bressolle F, Haug IJ, Galtier M, Blayac JP, Balmes P. Cisplatin-induced renal toxicity and toxicity-modulating strategies: a review. *Cancer Chemother Pharmacol* 1994;35:1–9.
- Clare MJ, Hydes PC, Malerbi BW, Watkins DM. Anti-tumor platinum complexes: relationships between chemical properties and activity. *Biochimie* 1978;60:835–50.
- du Bois A, Luck HJ, Meier W, Adams HP, Mobus V, Costa S, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst* 2003;95:1320–9.
- Cassidy J, Tabernero J, Twelves C, Brunet R, Butts C, Conroy T, et al. XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. *J Clin Oncol* 2004;22:2084–91.
- Horwich A, Sleijfer DT, Fossa SD, Kaye SB, Oliver RT, Cullen MH, et al. Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. *J Clin Oncol* 1997;15:1844–52.
- Bellmunt J, Ribas A, Eres N, Albanell J, Almanza C, Bermejo B, et al. Carboplatin-based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. *Cancer* 1997;80:1966–72.
- Nishiyama N, Okazaki S, Cabral H, Miyamoto M, Kato Y, Sugiyama Y, et al. Novel cisplatin-incorporated polymeric micelles can eradicate solid tumors in mice. *Cancer Res* 2003;63:8977–83.
- Uchino H, Matsumura Y, Negishi T, Hayashi T, Honda T, Nishiyama N, et al. Cisplatin-incorporating polymeric micelles (NC-6004) can reduce nephrotoxicity and neurotoxicity of cisplatin in rats. *Brit J Cancer* 2005;93:678–87.
- Wilson RH, Plummer R, Adam J, Eatock MM, Boddy AV, Griffin M, et al. Phase I and pharmacokinetic study of NC-6004, a new platinum entity of cisplatin-conjugated polymer forming micelles. *Am Soc Clin Oncol* 2008; (Abs# 2573).
- Li LH, Fraser TJ, Olin EJ, Bhuyan BK. Action of camptothecin on mammalian cells in culture. *Cancer Res* 1972;32:2643–50.
- Gallo RC, Whang-Peng J, Adamson RH. Studies on the antitumor activity, mechanism of action, and cell cycle effects of camptothecin. *J Natl Cancer Inst* 1971;46:789–95.
- Gottlieb JA, Guarino AM, Call JB, Oliverio VT, Block JB. Preliminary pharmacologic and clinical evaluation of camptothecin sodium (NSC-100880). *Cancer Chemother Rep* 1970;54:461–70.
- Muggia FM, Creaven PJ, Hansen HH, Cohen MH, Selawry OS. Phase I clinical trial of weekly and daily treatment with camptothecin (NSC-100880): correlation with preclinical studies. *Cancer Chemother Rep* 1972;56:515–21.
- Cunningham D, Pyrhonen S, James RD, Punt CJ, Hickish TF, Heikkila R, et al. Randomised trial of irinotecan plus supportive care versus supportive

- care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998;352:1413–8.
30. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000;343:905–14.
 31. Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002;346:85–91.
 32. Negoro S, Masuda N, Takada Y, Sugiura T, Kudoh S, Katakami N, et al., CPT-11 Lung Cancer Study Group West. Randomised phase III trial of irinotecan combined with cisplatin for advanced non-small-cell lung cancer. *Br J Cancer* 2003;88:335–41.
 33. Bodurka DC, Levenback C, Wolf JK, Gano J, Wharton JT, Kavanagh JJ, et al. Phase II trial of irinotecan in patients with metastatic epithelial ovarian cancer or peritoneal cancer. *J Clin Oncol* 2003;21:291–7.
 34. Takimoto CH, Arbus SG. Topoisomerase I targeting agents: the camptothecins. In: Chabner BA, Lango DL editors. *Cancer Chemotherapy and Biotherapy: Principal and Practice*, 3rd edn. Philadelphia (PA): Lippincott Williams & Wilkins 2001;579–646.
 35. Slatter JG, Schaaf LJ, Sams JP, Feenstra KL, Johnson MG, Bombardt PA, et al. Pharmacokinetics, metabolism, and excretion of irinotecan (CPT-11) following I.V. infusion of [(14)C]CPT-11 in cancer patients. *Drug Metab Dispos* 2000;28:423–33.
 36. Rothenberg ML, Kuhn JG, Burris HA, 3rd, Nelson J, Eckardt JR, Tristan-Morales M, et al. Phase I and pharmacokinetic trial of weekly CPT-11. *J Clin Oncol* 1993;11:2194–204.
 37. Guichard S, Terret C, Hennebelle I, Lochon I, Chevreau P, Fretigny E, et al. CPT-11 converting carboxylesterase and topoisomerase activities in tumor and normal colon and liver tissues. *Br J Cancer* 1999;80:364–70.
 38. Koizumi F, Kitagawa M, Negishi T, et al. Novel SN-38-incorporating polymeric micelles, NK012, eradicate vascular endothelial growth factor-secreting bulky tumors. *Cancer Res* 2006;66:10048–56.
 39. Sumitomo M, Koizumi F, Asano T, Horiguchi A, Ito K, Asano T, et al. Novel SN-38-incorporated polymeric micelles, NK012, strongly suppress renal cancer progression. *Cancer Res* 2008;122:2148–53.
 40. Saito Y, Yasunaga M, Kuroda J, Koga Y, Matsumura Y. Enhanced distribution of NK012 and prolonged sustained-release of SN-38 within tumors are the key strategic point for a hypovascular tumor. *Cancer Sci* 2008;99:1258–64.
 41. Nakajima-Eguchi T, Yanagihara K, Takigahara M, Yasunaga M, Kato K, Hamaguchi T, et al. Antitumor effect of SN-38-releasing polymeric micelles, NK012, on spontaneous peritoneal metastases from orthotopic gastric cancer in mice compared with irinotecan. *Cancer Res* 2008 (in press).
 42. Nakajima T, Yasunaga M, kano Y, Koizumi F, Kato K, Hamaguchi T, et al. Synergistic antitumor activity of the novel SN-38 incorporating polymeric micelles, NK012, combined with 5-fluorouracil in a mouse model of colorectal cancer, as compared with that of irinotecan plus 5-fluorouracil. *Int J Cancer* 2008;122:22148–53.
 43. Kato K, Hamaguchi T, Shirao K, Shimada Y, Yamada Y, Doi T, et al. Phase I study of NK012, polymer micelle SN-38, in patients with advanced cancer. *Am Soc Clin Oncol GI* 2008; (Abs#485).
 44. Burris HA, III, Infante JR, Spigel DR, Greco FA, Thompson DS, Matsumoto S, et al. A phase I dose-escalation study of NK012. *Am Soc Clin Oncol* 2008; (Abs#2538).