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Preclinical and clinical studies of NK012, an SN-38-incorporating polymeric micelles, which is designed based on EPR effect☆

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ABSTRACT

Polymeric micelles are ideally suited to exploit the EPR effect, and they have been used for the delivery of a range of anticancer drugs in preclinical and clinical studies.

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). The antitumor activity was evaluated in several orthotopic tumor models including glioma, renal cancer, stomach cancer, and pancreatic cancer. Two independent phase I clinical trials were conducted in Japan and the USA.

In the preclinical studies, it was demonstrated that NK012 exerted significantly more potent antitumor activity with no intestinal toxicity against various orthotopic human tumor xenografts than CPT-11. In clinical trials, predominant toxicity was neutropenia. Non-hematologic toxicity, especially diarrhea, was mostly Grade 1 or 2 during study treatments. Total 8 partial responses were obtained.

According to data of preclinical studies, NK012 showing enhanced distribution with prolonged SN-38 release may be ideal for cancer treatment because the antitumor activity of SN-38 is time dependent. Clinical studies showed that NK012 was well tolerated and had antitumor activity including partial responses and several occurrences of prolonged stable disease across a variety of advanced refractory cancers. Phase II studies are ongoing in patients with colorectal cancer in Japan and in patients with triple negative breast cancer and small cell lung cancer in the USA.

Contents

1. Preface

Irinotecan hydrochloride (CPT-11) is now approved for the treatment of various cancers including colorectal and lung cancers [1–4]. CPT-11 is a prodrug and is converted to SN-38, a biologically active metabolite of CPT-11, by carboxylesterases (CEs). SN-38 is an analog of the plant alkaloid camptothecin which targets DNA topoisomerase I. SN-38 exhibits up to 1000-fold more potent cytotoxic activity against various cancer cells in vitro than CPT-11 [5]. Although CPT-11 is converted to SN-38 in the liver and tumors, the metabolic conversion rate is less than 10% of the original volume of CPT-11 [6,7]. Moreover, the conversion of CPT-11 to SN-38 depends on the genetic inter-individual variability of CE activity [8]. Thus, further efficient use of SN-38 might be

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Table 1
Example of other DDS of campto in oncolgy.

Name	Platform	Clinical stage
NKTR-102	PEG	Phase II
PEP02	Liposome	Phase II
CPX-1	Liposome	Phase II
IT-101	Cyclodextrin	Phase II
EZN-2208	Branch-PEG	Phase II
SN-2310	Vitamin E	Phase I
IHL-305	Liposome	Phase I

of great advantage and maybe attractive for cancer treatment. To date, many DDS of campto have been developed and some of them are now under clinical evaluation (Table 1). Polymeric micelle-based anticancer drugs were originally developed by Kataoka et al. in the late 1980s or early 1990s [9–11]. Polymeric micelles were expected to increase the accumulation of drugs in tumor tissues by utilizing the EPR effect [12]. Micelle system can also incorporate various kinds of drugs into their inner core with relatively high stability by chemical conjugation or physical entrapment. Also, the size of micelles can be controlled within the diameter range of 20 to 100 nm to ensure that they do not penetrate normal vessel walls. With this development, it is expected that the incidence of drug-induced side effects may be decreased owing to the reduced drug distribution in normal tissues. 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) [13].

In this paper, preclinical and clinical studies of NK012 were reviewed.

2. Preparation of an SN-38 conjugated poly(ethylene glycol)–poly (glutamic acid) block copolymer [PEG–PGlu(SN-38)] for NK012 construction

PEG–PGlu(SN-38) was synthesized as follows: a poly(ethylene glycol)–poly(glutamic acid) block copolymer [PEG–PGlu] was prepared according to the technique reported previously [14,15]. SN-38 was covalently introduced into the poly(glutamic acid) [PGlu] segment by the condensation reaction between the carboxylic acid on PGlu and the phenol on SN-38 with 1,3-diisopropylcarbodiimide and N,N-dimethylaminopyridine at 26 °C. Consequently, the poly(glutamic acid) segment obtained sufficient hydrophobicity. Accordingly, NK012 was constructed with self-assembling PEG–PGlu(SN-38), amphiphilic block copolymers, in an aqueous milieu. NK012 was obtained as a freeze-dried formulation and contained ca. 20% (w/w) of SN-38 (Fig. 1). The mean particle size of NK012 is 20 nm in diameter with a relatively narrow range. The percentage released of SN-38 from NK012 in phosphate buffered saline at 37 °C were 57% and 74% at 24 h and 48 h, respectively, and that in 5% glucose solution at 37 °C were 1% and 3% at 24 h and 48 h, respectively. These results indicate that NK012 can release SN-38 under neutral condition even without the presence of a hydrolytic enzyme, and is stable in 5% glucose solution. In the formulation of NK012, SN-38 is bound to carboxyl group of hydrophobic chain of the block copolymer via ester bond and hydrolyzed to release SN-38. This ester bond may be cut gradually but efficiently at weak basic condition (PBS, pH 7.4) but very stable at weak acidic condition (5% glucose, pH 4.0). Consequently, it is suggested that NK012 is stable before administration and starts to release SN-38, the active component, inside a tumor following the accumulation of micelles into tumor tissue by utilizing the EPR effect.

3. Preclinical studies

3.1. Pancreatic cancer

Human pancreatic cancer is well known to have the worst prognosis [16]. At the time of diagnosis, the vast majority of the cancer extends beyond the pancreas. Direct invasion to nearby organs such as the stomach, duodenum, colon, spleen, and kidney is common. Distant metastasis to the liver and peritoneal dissemination are also common [17,18]. Gemcitabine is a first-line therapy for patients with advanced pancreatic cancer; however, only a response rate within 6–11% was

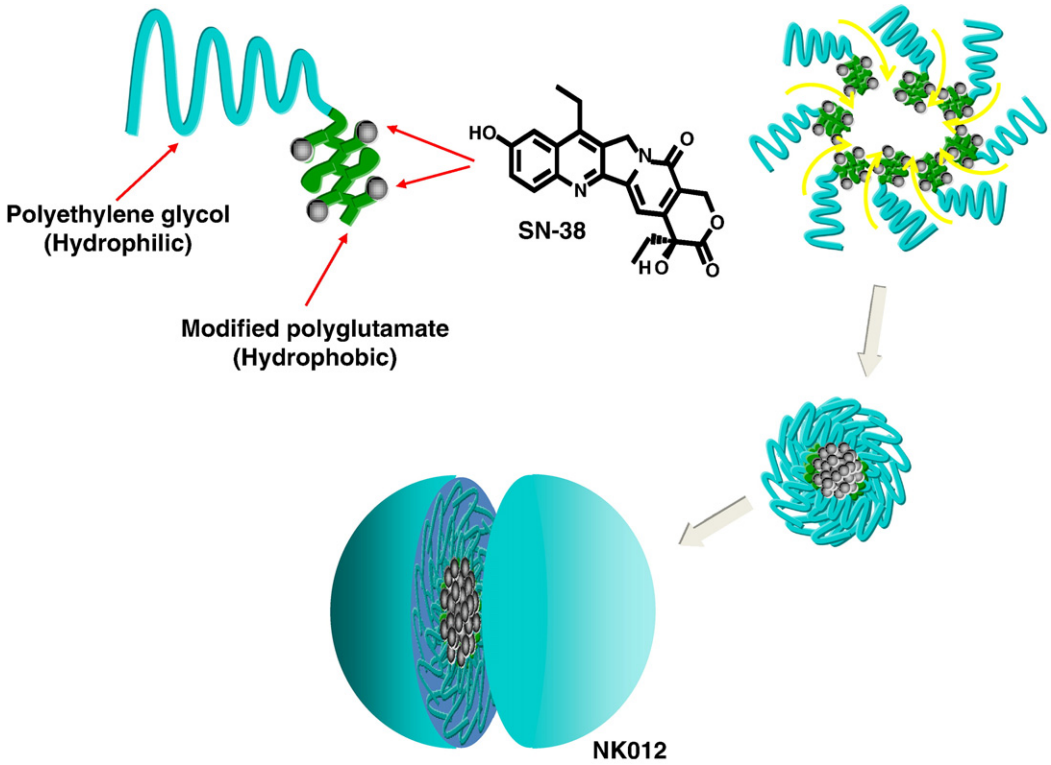

Fig. 1. Schematic structure of NK012. A polymeric micelle carrier of NK012 consists of a block copolymer of PEG (molecular weight of about Mw. 12,000 Da) and partially modified polyglutamate (about 20 units). Polyethylene glycol (hydrophilic) is believed to be the outer shell and SN-38 was incorporated into the inner core of the micelle.