(24) Mathijssen, R. H., van Alphen, R. J., Verweij, J., Loos, W. J., Nooter, K., Stoter, G., and Sparreboom, A. (2001) Clinical pharmacokinetics and metabolism of irinotecan (CPT-11). *Clin. Cancer Res. 7*, 2182–2194.

(25) Senter, P. D., Beam, K. S., Mixan, B., and Wahl, A. F. (2001) Identification and activities of human carboxylesterases for the activation of CPT-11, a clinically approved anticancer drug. *Bioconjugate Chem. 12*, 1074–1080.

(26) Zhao, H., Rubio, B., Sapra, P., Wu, D., Reddy, P., Sai, P., Martinez, A., Gao, Y., Lozanguiez, Y., Longley, C., Greenberger, L. M., and Horak, I. D. (2008) Novel prodrugs of SN38 using multiarm poly(ethylene glycol) linkers. *Bioconjugate Chem. 19*, 849–859.

(27) Naito, S., von Eschenbach, A. C., and Fidler, I. J. (1987) Different growth pattern and biologic behavior of human renal cell carcinoma implanted into different organs of nude mice. *J. Natl. Cancer Inst. 78*, 377–385.

(28) Fallowfield, M. E. (1989) Blood flow distribution within transplantable tumors in the mouse. *Eur. J. Cancer Clin. Oncol. 25*, 1683–1688.

(29) Doronina, S. O., Torgov, M. Y., Mendelsohn, B. A., Cerveny, C. G., Chace, D. F., DeBlanc, R. L., Gearing, R. P., Bovee, T. D., Siegall, C. B., Francisco, J. A., Wahl, A. F., Meyer, D. L., and Senter, P. D. (2003) Development of potent monoclonal antibody auristatin conjugates for cancer therapy. *Nat. Biotechnol. 21*, 778–784.

(30) Wu, A. M., and Senter, P. D. (2005) Arming antibodies: Prospects and challenges for immunoconjugates. *Nat. Biotechnol. 23*, 1137–1146.

(31) Baluk, P., Morikawa, S., Haskell, A., Mancuso, M., and McDonald, D. M. (2003) Abnormalities of basement membrane on blood vessels and endothelial sprouts in tumors. *Am. J. Pathol. 163*, 1801–1815.

(32) Folkman, J. (2007) Angiogenesis: An organizing principle for drug discovery?. *Nat. Rev. Drug Discovery 6*, 273–286.

(33) Wahl, A. F., Donaldson, K. L., Mixan, B. J., Trail, P. A., and Siegall, C. B. (2001) Selective tumor sensitization to taxanes with the mAb-drug conjugate cBR96-doxorubicin. *Int. J. Cancer 93*, 590–600.

(34) Doronina, S. O., Bovee, T. D., Meyer, D. W., Miyamoto, J. B., Anderson, M. E., Morris-Tilden, C. A., and Senter, P. D. (2008) Novel peptide linkers for highly potent antibody-auristatin conjugate. *Bioconjugate Chem. 19*, 1960–1963.

(35) Burris, H. A., 3rd., Rugo, H. S., Vukelja, S. J., Vogel, C. L., Borson, R. A., Limentani, S., Tan-Chiu, E., Krop, I. E., Michaelson, R. A., Girish, S., Amler, L., Zheng, M., Chu, Y. W., Klencke, B., and O'Shaughnessy, J. A. (2011) Phase II Study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. *J. Clin. Oncol. 29*, 398–405.

Invest New Drugs (2012) 30:1621–1627
DOI 10.1007/s10637-011-9709-2

PHASE II STUDIES

Phase II study of NK105, a paclitaxel-incorporating micellar nanoparticle, for previously treated advanced or recurrent gastric cancer

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Received: 25 April 2011 / Accepted: 21 June 2011 / Published online: 5 July 2011
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Summary *Purpose* NK105 is a new drug delivery system formulation for paclitaxel (PTX) whose recommended dose (RD) is 150 mg PTX equivalent/m^2 administered every 3 weeks, as determined in a phase I trial. This study aimed to evaluate the efficacy and safety of NK105 in patients with advanced gastric cancer after failure of first-line chemotherapy. *Experimental design* Eligible patients had measurable disease and one chemotherapeutic regimen except taxane. NK105 (150 mg PTX equivalent/m^2) was administered by a 30-minute intravenous infusion every 3 weeks without anti-allergic premedication until disease progression, unacceptable toxicity or patient refusal. The primary efficacy endpoint was best overall response rate (ORR) post baseline. The secondary endpoints were progression-free survival (PFS), time to treatment failure (TTF) and overall survival (OS). All adverse events were reported using CTCAE v3.0. *Results* Between November 2007 and July 2009, 57 patients were enrolled and 56 were evaluable for efficacy. Two complete responses and 12 partial responses were observed for an ORR of 25%. The median PFS was 3.0 months, the median TTF was 2.8 months, and the median OS was 14.4 months. Drug related toxicity was mainly mild (grades 1–2) to severe (grades 3–4); other data: neutropenia (64.9%); leukopenia (17.5%); lymphopenia (8.8%); neuropathy-sensory (1.8%); fatigue (3.5%); and stomatitis (1.8%). There were no treatment-related deaths. *Conclusions* This study of NK105 (150 mg PTX equivalent/m^2) proves the concept for the modest activity and tolerability of a new drug delivery system formulation for PTX. A phase III trial will be evaluated to clarify survival benefit.

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Keywords NK105 · Micellar nanoparticle · Phase II study · Gastric cancer · Second line

Introduction

Gastric cancer has a high incidence rate in Asia and Eastern Europe, and is the fourth most common cancer with 933,937 new cases reported annually as of 2002 [1]. Despite a continuous decline in incidence, gastric cancer remains the second leading cause of cancer-related deaths with an estimated 700,349 deaths annually [1]. In Japan, gastric cancer is the second leading cause of cancer deaths with 50,160 new cases in 2008, accounting for 15.3% of all cancer deaths [2].

Although surgical resection is the only curative treatment for gastric cancer, two-thirds of patients are usually diagnosed in the advanced or metastatic stage. Furthermore, 50% of patients experience a relapse after curative resection. Systemic chemotherapy has been investigated for decades aiming at improving the survival time of metastatic or recurrent gastric cancer patients. Fluoropyrimidine in combination with a platinum agent was mainly used as first-line chemotherapy worldwide, and this combination has been investigated in most of the recently completed phase III clinical trials, showing a median survival time of 10–13 months [3–7]. There is little evidence of the survival benefit of second-line chemotherapy, although some reports based on retrospective analysis have shown its potential [8]. Furthermore, second-line irinotecan showed survival benefit compared with best supportive care (BSC) after failure of fluoropyrimidine-based therapy in a randomized trial [9]. However, only a small number of patients (30–60%) receive this second-line chemotherapy in every clinical practice because of their poor condition following first-line chemotherapy [10, 11]. In Japan, weekly paclitaxel (PTX) is commonly used as second-line chemotherapy for gastric cancer, showing a response rate of 16–20% and an overall survival (OS) time of 5–7 months with modest toxicity [12, 13].

PTX has a wide spectrum of antitumor activity including ovarian, breast, gastric and lung cancers [14–16]. The clinically used PTX preparation is a mixture of Cremophor EL because of PTX's poor water solubility. However, the use of Cremophor EL is associated with acute hypersensitivity reactions [17–19]. NK105 is a PTX-incorporating 'core-shell-type' polymeric micellar nanoparticle formulation [20]. The nanoparticle can be injected intravenously without using Cremophor EL as a vehicle. Therefore, NK105 is expected to possess a clinical advantage over PTX. On the other hand, macromolecular drugs, including NK105, are developed based on the characteristic macroscopic features of solid tumors such as hypervasculature, presence of vascular permeability factors stimulating extravasation within the cancer, and suppressed lymphatic clearance of macromolecules. These characteristics unique to solid tumors constitute the basis of the enhanced permeability and retention (EPR) effect [21, 22]. Notably, the in vivo antitumor activity of NK105 was significantly more potent than that of free PTX. In a phase I study, the recommended dose was 150 mg/m^2 administered every 3 weeks [23]. This was less than that of conventional PTX; however, the plasma area under the curve (AUC) of the recommended dose of NK105 was 15-fold higher than that of conventional PTX (210 mg/m^2). Moreover, hematological and non-hematological toxicities of NK105 were mild and well manageable. In particular, there was no grade 3 peripheral neuropathy even in patients who received more than 5 cycles of NK105. However, these results were only obtained from a small number of patients and therefore a larger population and longer treatment duration need to be evaluated.

This phase II clinical trial using NK105 in patients who were unresponsive to the first-line treatment of gastric cancer was therefore conducted. The specific objectives were to determine the response rate, progression-free survival (PFS), OS, time to treatment failure, and toxicity of NK105.

Patients and methods

Patient eligibility

An open-label, single-arm, multicenter, phase II study was conducted and included patients ≥20 and <75 years of age with pathologically confirmed advanced gastric carcinoma who had received one prior chemotherapy regimen except taxanes, and who had one or more measurable lesions according to the Response Evaluation Criteria in Solid Tumor (RECIST) [24]. Failure (disease progression/discontinuation due to toxicity) within 6 months of the last dose of first-line fluoropyrimidine and/or cisplatin treatment for metastatic disease or adjuvant therapy was required. Before study entry, previous therapies had to be completed for ≥2 weeks for fluoropyrimidine and an immunosuppressive agent, and ≥4 weeks for other chemotherapy, surgery or radiotherapy. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2 and adequate organ function (bone marrow function: neutrophils ≥2000/mm^3, platelets ≥10×10^4/mm^3; liver function: serum bilirubin ≤1.8 mg/dL and ALT and AST ≤2.5× the upper limit of normal; renal function: serum creatinine ≤.5 mg/dL). Exclusion criteria were as follows: already detected CNS metastasis, malignant ascites requiring invasive treatment, peripheral neuropathy of at least grade 2, or

severe uncontrolled medical conditions (e.g., impaired heart and lung function, active infection or liver disease). Written informed consent was obtained from all the patients. The study protocol was approved by the institutional review boards of the participating institutions. Financial support was provided by Nippon Kayaku Co., Ltd. (Tokyo, Japan).

Study treatment and assessment

NK105 was supplied by Nippon Kayaku Co., Ltd. (Tokyo, Japan) in 20-mL glass vials containing a dose equivalent to 30 mg of PTX. A previous phase I trial determined the recommended NK105 dose as 150 mg PTX equivalent/m^2 administered every 3 weeks [23]. NK105 was dissolved in 100 mL of 5% glucose and intravenously administered within 30 min without any pre-medication for hypersensitivity. Before each cycle, the patients had no grade ≥2 toxicity. Treatment was terminated if disease progression or severe toxicity was observed. The NK105 dose was reduced to 120 mg/m^2 or 100 mg/m^2 if patients experienced grade 4 neutropenia lasting more than 7 days, grade 4 thrombocytopenia, grade 3 non-hematological toxicity or considerable grade 2 neurosensory toxicity.

Tumor assessment by computed tomography was performed within 4 weeks before registration to this study and repeated every 6 weeks. Overall response rates (ORRs) were evaluated in accordance with RECIST [24]. If the response was observed, CT scans were taken 4 weeks later to confirm the response. Tumor responses were confirmed by an external review committee (ERC). PFS was defined as the duration from the date of the first dose of the study drug to the date of the first confirmation of disease progression as determined by the ERC, or death from any cause, and censored at the last tumor assessment. Time to treatment failure (TTF) was defined as the time from the administration of the first dose of the study drug to the discontinuation of the protocol treatment. OS was defined as the duration from the first dose of the study drug to death.

Adverse events were evaluated weekly in accordance with the Common Terminology Criteria for Adverse Event, version 3.0 [25]. All adverse events were evaluated until 21 days after the last dose of the study drug.

For pharmacokinetics (PK) analysis, blood samples were collected from the first 6 patients before the first dose and 15 and 30 min, 1, 3, 6 and 24 h, 3 days, and 1 week after the first dose in the first cycle. Plasma level of PTX (both micelle-entrapped and released) was measured by liquid chromatography/tandem mass spectrometry. A non-compartmental model using the WinNonlin Professional Ver. 5.2 program (Pharsight Corp., St. Louis, MO, USA) was used to determine the PK parameters of AUC, maximum plasma drug concentration (Cmax), time to reach maximum concentration after drug administration (Tmax) and half-life of the terminal phase ($t_{1/2}$).

Statistical analysis

The primary study endpoints were overall response rate (ORR) as assessed by the ERC. The standard Southwest Oncology Group phase II design was adopted [26], selecting an alpha error of 0.05 and a beta error of 0.10. The minimum activity required for this experimental treatment was 16%, while the alternative hypothesis was to obtain a 33% response rate. Therefore, the accrual had to be stopped if there were less than 4 responses with the first 30 patients, in which an additional 25 patients were planned to be enrolled. Fifty-five patients were required to test the null hypothesis. The secondary endpoints were PFS, TTF, OS, and safety. PFS, TTF, and OS were estimated using the Kaplan-Meier (product-limit) method with 95% confidence interval (CI).

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all patients who participated. The protocol was approved by the independent ethics committee or institutional review board at each site.

Results

Patient characteristics

All 57 patients enrolled between November 2007 and July 2009 were included in the safety analysis; however, 1 was excluded from the efficacy analysis because this patient had no measurable lesion. Therefore, 56 patients were included in the efficacy evaluation of NK105 (Fig. 1). At the data cut-off date (January 7, 2010), 54 patients had discontinued the protocol treatment for the following reasons: disease progression (n=50), adverse events (n=3), and patient

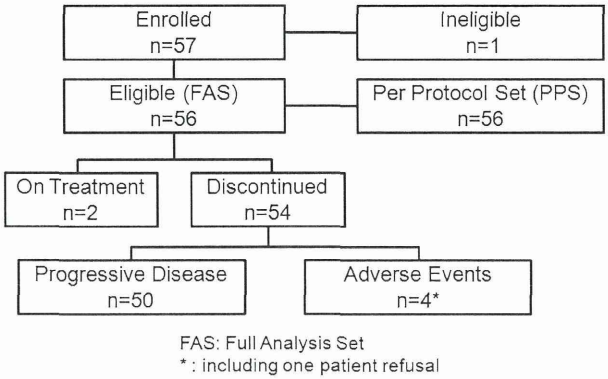

Fig. 1 CONSORT diagram of 57 patients

Table 1 Baseline demographic characteristics

Characteristic	Number of patients	Percentage
Sex		
Male	39	69.6
Female	17	30.4
Age (years)		
Median	63.5	
Range	25–74	
ECOG performance status		
0	43	76.8
1	12	21.4
2	1	1.8
Histologic type		
Intestinal	30	53.6
Diffuse	25	44.6
Unknown	1	1.8
Gastrectomy		
Yes	35	62.5
No	21	37.5
Adjuvant chemotherapy		
S-1	9	16.1
S-1/CDDP	2	3.6
others	2	3.6
Prior chemotherapy		
S-1	9	16.1
S-1/CDDP	24	42.9
Others	10	17.9

ECOG, Eastern Cooperative Oncology Group

refusal (n=1). The baseline demographic characteristics of the enrolled study patient population are shown in Table 1. Most patients were men (69.6%) with a median age of 63.5 years (range, 25–74). The ECOG PS was 0 in 43 patients, 1 in 12, and 2 in 1. Twenty-one (37.5%) patients had primary unresectable advanced gastric cancer and 35 (62.5%) had recurrence after gastrectomy. All patients received prior chemotherapy, namely, an S-1-containing regimen (78.6%) and others (21.4%). The median progression free survival of first line treatment was 6.4 month.

Treatment duration

The median treatment duration was 2.8 months (range, 0.5–18.5) with a median treatment cycle of 4 (range, 1–28). After NK105 discontinuation, 46 patients (82.1%) received chemotherapy with irinotecan-based regimens (37), whereas 5 continued to receive the protocol treatment or were lost to follow up. Five patients have had BSC rather than chemotherapy. The mean relative dose intensity (ratio of the dose received to the dose planned) was 95.1% for NK105.

Efficacy

At the final data cut-off date (January 7, 2010), the median follow-up duration was 11.3 months (range, 6.0–22.0).

The results of efficacy analysis are shown in Table 2. The ORR was 25% (95% CI: 14.4–38.4%). The median time to response and the duration of response were 1.8 and 3.7 months, respectively. The median PFS, median OS, and median TTF were 3.0 months (95% CI: 2.6–5.3), 14.4 months (95% CI: 12.6–15.9), and 2.8 months (95% CI: 2.5–4.9), respectively (Figs. 2 and 3).

Safety

The major adverse events observed with NK105 were grade 1 or 2 in severity (Table 3). The most common adverse events were alopecia (87.7%), peripheral neuropathy (64.9%), fatigue (57.9%), myalgia (59.6%), anorexia (47.4%), rash (49.1%), althralgia (45.6%), stomatitis (31.6%), diarrhea (22.8%), and nausea (28.1%). The most common grade 4 hematological toxicities were neutropenia (24.6%), anemia (1.8%), leukocytopenia (1.8%), and lymphopenia (1.8%). Grade 3/4 non-hematological toxicities were infrequent, with fatigue (3.5%) and peripheral neuropathy (1.8%). Neutropenic fever was not seen. Although NK105 was administered without any premedication, there were no patients who experienced grade 3/4 hypersensitive reaction.

Dose reductions to reduce toxicity were performed in 7 patients (12.3%). There were 6 serious adverse events

Table 2 Overall response rate

	n	CR	PR	SD	PD	NE	ORR (CR+PR) (95%CI)	DCR (CR+PR+SD) (95%CI)
All patients	56	2	12	17	25	0	25.00% (14.4–38.4)	55.4% (41.5–68.7)
Histologic type								
Intestinal	30	0	6	11	13	0	20.00%	56.70%
Diffuse	25	2	6	6	11	0	32.00%	56.00%
Unknown	1	0	0	0	1	0	0.00%	0.00%

CR complete response
PR partial response
SD stable disease
PD progressive disease
NE not evaluable
ORR overall response rate
DCR disease control rate

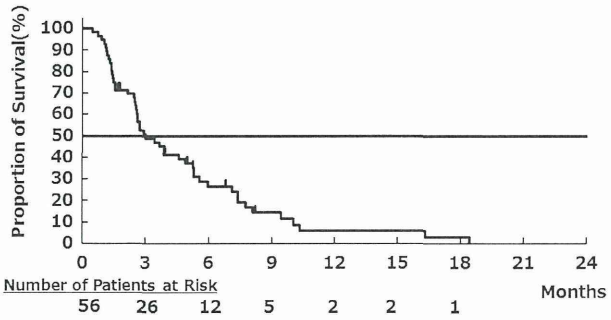

Fig. 2 Progression-free survival of 56 patients

related to NK105 in 2 patients: pneumonia (n=1) and fever (n=1). There were no treatment-related deaths.

Pharmacokinetics

Plasma PTX concentration after the intravenous infusion of NK105 was determined in each of the first 6 patients enrolled in this study. The AUC of NK105 at 150 mg/m^2 was 214±10 μg hr/mL, which was about 9-fold larger than that of conventional PTX at dose of 210 mg/m^2 (conventional dose for every 3 weeks) [27]. The V_{ss} and CL_{tot} of NK105 were significantly lower than those of conventional PTX. These PK parameters were almost similar to those observed in the phase I study.

Discussion

In the present study, we showed that NK105 has activity against advanced gastric cancer with an ORR of 25%, including previously treated gastric cancer with 2 CR cases. However the ORR which is the primary endpoint of this study did not meet the hypothesis, 64.3% of 14 responders in the present trial showed no response to the first-line chemotherapy. Response rates do not always correlate with improved survival as an ultimate goal, particularly for intractable cancers (e.g., gastric cancer). Therefore, the clinical benefit observed in this trial in which 30.4% of the

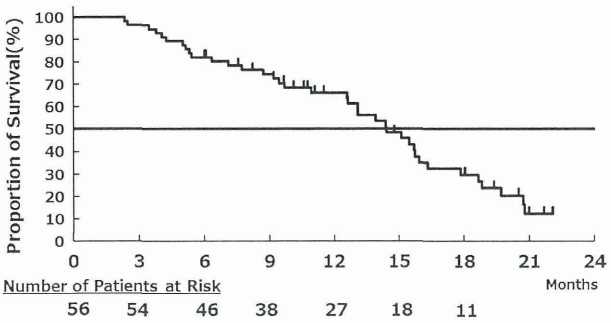

Fig. 3 Overall survival of 56 patients

Table 3 Incidence of common adverse event

Adverse Drug Reaction	Safety analysis set (N=57)					
	Number of patients				All	Grade 3/4
	Grade 1	Grade 2	Grade 3	Grade 4	%	%
Leukocytepenia	12	27	9	1	86	17.5
Neutropenia	5	10	23	14	91.2	64.9
Anemia	5	19	6	1	54.4	12.3
Lymphopenia	16	8	4	1	50.9	8.8
Platelet	15	1	0	0	28.1	0
Anorexia	22	5	0	0	47.4	0
Nausea	15	1	0	0	28.1	0
Diarrhea	11	2	0	0	22.8	0
Stomatitis	15	2	1	0	31.6	1.8
Fatigue	24	7	2	0	57.9	3.6
Arthralgia	22	4	1	0	45.6	1.8
Myalgia	32	2	0	0	59.6	0
Neurosensory toxicity	29	7	1	0	64.9	1.8
Alopecia	34	16	–	–	87.7	0
Rash	23	4	1	0	49.1	1.8
ALT	13	1	0	0	24.6	0
AST	16	2	0	0	31.6	0
G-GTP	9	3	0	0	21.1	0

enrolled patients achieved stable disease for several months is remarkable. Consequently, the disease control rate was 55.4%, which is promising for previously treated patients with advanced gastric cancer. Therefore, the median OS (14.4 months; 95% CI: 12.6–15.9 months) in this study is also reasonably promising.

Although there are several active regimens in the second-line therapy for gastric cancer [11], there is no standard therapy for advanced gastric cancer that has progressed after the initial fluoropyrimidine and cisplatin-based treatment. There is, therefore, an urgent need to develop new regimens that can provide a significant benefit to patients. Several drugs have been investigated in phase II studies for the second-line treatment of gastric cancer, with response rates ranging between 12.5% and 31.8% [11].

NK105 was generally well tolerated and its toxicity features were similar to those of conventional PTX. The most common hematological toxicity was neutropenia. Grade 3 or 4 neutropenia and anemia accounted for 64.9% and 12.3%, respectively, but all hematological toxicities were manageable throughout this study. Non-hematological toxicities were mild and grade 3 at worst. During the entire study, only 1 patient experienced grade 3 neuropathy (1.8%). The incidence rates of grade 3 or 4 neuropathy of other PTX formulations, namely, conventional PTX [27], Opaxio [28], a PTX conjugating poly-L-

glutamic acid, and Abraxane [29, 30], an albumin bound PTX, were 10%, 15%, and 11%, respectively, in each phase II setting. The incidence rates of other major grade 3 non-hematological toxicities were also low, which included 1 stomatitis (1.8%), 2 fatigue (3.6%), 1 arthralgia (1.8%), and 1 rash (1.8%). As patients with advanced gastric cancer suffer from marked anorexia, fatigue, constipation, weight loss, and other conditions, a favorable feature of NK105 is that its induces a lower incidence of gastrointestinal toxicity.

The PK analysis of NK105 in both phase II and the previous phase I studies suggests that the distribution of PTX-incorporating micelles is mostly restricted to the plasma and, in part, to extracellular body fluids. When compared with conventional PTX at a dose of 210 mg/m^2 (conventional 3-week regimen dose), NK105 at a dose of 150 mg/m^2 exhibited more than 9-fold larger plasma AUC and a 26-fold lower CL_{tot}. Specifically, the increased AUC and prolonged release of active paclitaxel from the micelle formulation might produce good efficacy. It is speculated that NK105 preferentially accumulated in tumor tissue utilizing leaky tumor vessels. On the other hand, the Vss of NK105 was more than 10-fold lower than that of conventional PTX, suggesting that PTX may have a relatively lower distribution in normal neural tissue following NK105 administration. Lower distribution in normal tissue caused less toxicity of NK105 than the other paclitaxel formulations. On the other hands, modest anti-tumor activity of NK105, in spite of the larger AUC, may be caused by the hypo-vascular environment of gastric cancer cell.

Formulations categorized in DDS have been developed with some already approved for clinical use or are under clinical evaluation. These preparations include Opaxio (polyglutamate-conjugated PTX) [28] and Abraxane (albumin-coated PTX) [29, 30]. Since PTX is highly water-insoluble, a mixture of Cremophor EL and ethanol must be used to dissolve PTX for injection. However, the use of Cremophor EL is associated with acute hypersensitivity reactions [17–19]. The common advantage of these formulations categorized in DDS is that they are injectable intravenously without the mixture of Cremophor EL and ethanol. The present trial showed that NK105 could be dissolved in 5% glucose solution without Cremophor EL and ethanol, and administered safely at a short infusion time (30 min) without any anti-allergic agents.

In conclusion, NK105 appeared to be very efficacious without compromising the antitumor activity of PTX in patients with previously treated advanced gastric cancer. While we understand at the moment that it is challenging to make direct comparisons between our data of NK105 and the published reports of other PTX formulations, some observations can be made and we believe that the present results warrant further clinical evaluation including a comparison with other clinically available taxanes.

Acknowledgments of research support We thank all the patients and families who participated in this trial. We are indebted to Dr. Ichinosuke Hyodo, Dr. Kuniaki Shirao, and Dr. Hirohumi Fujii for their help in the assessment of efficacy and evaluation of safety. This work was funded by Nippon Kayaku Co., Ltd. (Tokyo, Japan).

References

1. GLOBOCAN database http://www-dep.iarc.fr/globocan/globocan.html.
2. Vital Statistics Japan (Ministry of Health, Labour and Welfare)
3. Boku N, Yamamoto S, Fukuda H et al (2009) Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol 10:1063–1069
4. Al-Batran SE, Hartmann JT, Probst S et al (2008) Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 26:1435–1442
5. Koizumi W, Narahara H, Hara T et al (2008) S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 9:215–221
6. Van Cutsem E, Moiseyenko VM, Tjulandin S et al (2006) Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study group. J Clin Oncol 24:4991–4997
7. Cunningham D, Starling N, Rao S et al (2008) Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 358:36–46
8. Hashimoto K, Takashima A, Nagashima K et al (2009) Progression-free survival in first-line chemotherapy is a prognostic factor in second-line chemotherapy in patients with advanced gastric cancer. J Cancer Res Clin Oncol 136:1059–1064
9. Thuss-Patience PC, Kretzschmar A, Deist T, et al (2009) Irinotecan versus best supportive care (BSC) as second-line therapy in gastric cancer: a randomized phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). J Clin Oncol;27:15s, (suppl; abstr 4540).
10. Wilson D, Hiller L, Geh JI (2005) Review of second-line chemotherapy for advanced gastric adenocarcinoma. Clin Oncol 17:81–90
11. Wesolowski R, Lee C, Kim R (2009) Is there a role for second-line chemotherapy in advanced gastric cancer? Lancet Oncol 10:903–912
12. Kodera Y, Ito S, Mochizuki Y et al (2007) Phase II study of weekly paclitaxel as second-line chemotherapy for advanced gastric cancer (CCOG0302 study). Anticancer Res 27:2667–2671
13. Hironaka S, Zenda S, Boku N et al (2006) Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. Gastric Cancer 9:14–18
14. Rowinsky EK, Cazenave LA, Donehower RC (1990) Taxol: a novel investigational antimicrotubule agent. J Natl Cancer Inst 82:1247–1259
15. Carney DN (1996) Chemotherapy in the management of patients with inoperable non-small cell lung cancer. Semin Oncol 23:71–75
16. Crown J, O'Leary M (2000) The taxanes: an update. Lancet 355:1176–1178

17. Weiss RB, Donehower RC, Wiernik PH et al (1990) Hypersensitivity reactions from taxol. J Clin Oncol 8:1263–1268
18. Rowinsky EK, Donehower RC (1995) Paclitaxel (taxol). N Engl J Med 332:1004–1014
19. Kloover JS, den Bakker MA, Gelderblom H et al (2004) Fatal outcome of a hypersensitivity reaction to paclitaxel: a critical review of premedication regimens. Br J Cancer 90: 304–305
20. Hamaguchi T, Matsumura Y, Suzuki M et al (2005) NK105, a paclitaxel-incorporating micellar nanoparticle formulation, can extend in vivo antitumour activity and reduce the neurotoxicity of paclitaxel. Br J Cancer 92:1240–1246
21. Matsumura Y, Maeda H (1986) A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer Res 46:6387–6392
22. Maeda H, Wu J, Sawa T et al (2000) Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. J Control Release 65:271–284
23. Hamaguchi T, Kato K, Yasui H (2007) A Phase I and pharmacokinetic study of NK105, a paclitaxel -incorporating micellar nanoparticle formulation. Br J Cancer 97:170–176
24. Therasse P, Arbuck S, Eisenhauer E et al (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205–216
25. Common Terminology Criteria for Adverse Event (CTC-AE Version 3.0, March 31, 2003).
26. Green S, Dahlberg S (1992) Planned versus attained design in Phase II clinical trials. Stat Med 11:853–862
27. Tamura T, Sasaki Y, Nishiwaki Y, Saijo N (1995) Phase I study of paclitaxel by three-hour infusion: Hypotension just after infusion is one of the major dose-limiting toxicities. Jpn J Cancer Res 86:1203–1209
28. Boddy AV, Plummer ER, Todd R et al (2005) A phase I and pharmacokinetic study of paclitaxel poliglumex (XYOTAX), investigating both 3-weekly and 2-weekly schedules. Clin Cancer Res 11:7834–7840
29. Ibrahim NK, Desai N, Legha S et al (2002) Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. Clin Cancer Res 8:1038–1044
30. Gradishar WJ, Tjulandin S, Davidson N et al (2005) Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 23:7794–7803

Advanced Drug Delivery Reviews 64 (2012) 710–719

Contents lists available at SciVerse ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Cancer stromal targeting (CAST) therapy☆

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ARTICLE INFO

Article history:
Received 26 August 2011
Accepted 16 December 2011
Available online 24 December 2011

Keywords:
Cancer stromal targeting
Blood coagulation
Fibrin
Collagen 4
Immunoconjugate

ABSTRACT

Despite great advances in cell and molecular biology, pharmacology and medicine, there is to date no antitumor drug available which can specifically kill tumor cells in the human body without damaging normal tissue, because it has not been possible to find a truly cancer specific molecule to target.
Low molecular weight (MW) anticancer drugs extravasate easily from normal vessels in the body causing drug adverse effects. Conversely, high MW anti-tumor agents including antibodies against cancer cell antigens, accumulate selectively in tumors because of their leaky vasculature. However, most human solid tumors possess abundant intercellular connective tissue, hindering diffusion of such macromolecules. That is why immunoconjugate therapy for stroma rich common solid cancer has not yet proved successful in clinics. In this review, I describe a successful new strategy that overcomes the above contradictory drawbacks by conjugating a small MW cyototoxic drug with an antibody against particular components of tumor stroma. Stroma-targeting immunconjugates bound to the stroma to create a scaffold, from which sustained release of cytotoxic agent occurred and subsequently diffused throughout the tumor tissue to damage both tumor cells and tumor vessels. Cancer-stroma targeting (CAST) therapy was thus validated as a new modality of oncological therapy, especially for refractory, stromal-rich cancers.

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Contents

1. Preface

Conventional low molecular weight (LMW) anticancer agents (ACA) including molecular targeting agents can easily extravasate from normal blood vessels and are distributed throughout the whole body leading to adverse effects of the drugs (Fig. 1A). In order to overcome such off-target effects caused by LMW ACAs, formulations categorized in drug delivery system (DDS) have been developed to achieve selective delivery of ACAs to cancer tissue at an effective concentration for the appropriate duration of time, so that we may be able to reduce the adverse effects of a LMW drug and simultaneously enhance the antitumor effect.

There are two main concepts in DDS, active targeting and passive targeting. Active targeting involves monoclonal antibodies (mAb) or ligands to tumor related receptors which can target the tumor by

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Therapeutic Strategies for Controlling Metastasis and Recurrence of Cancers; Contribution of Drug Delivery Technologies".

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doi:10.1016/j.addr.2011.12.010

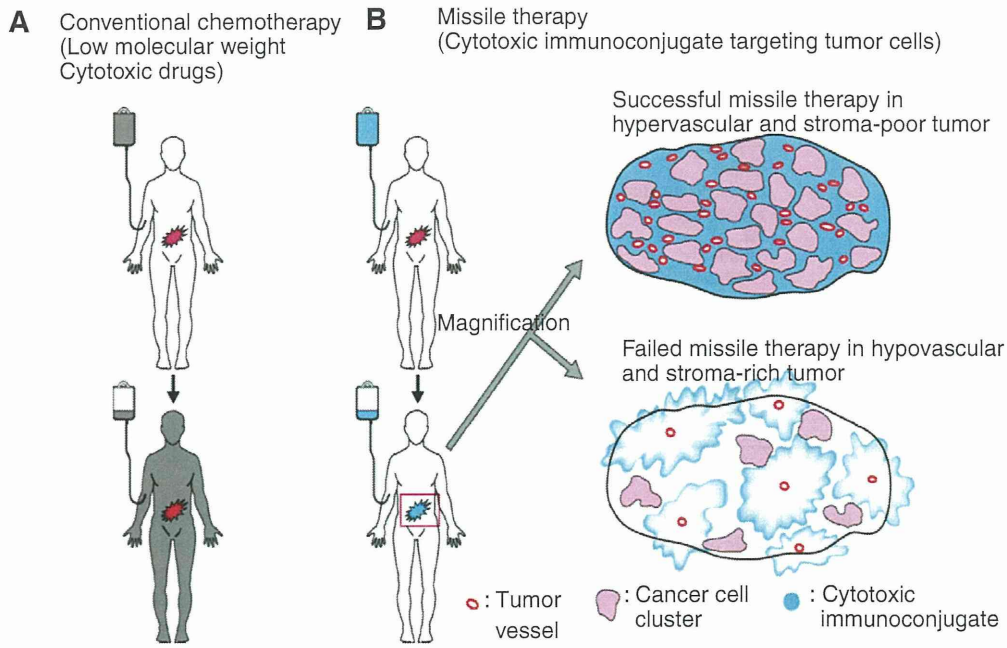

Fig. 1. Drawback of so-called missile therapy. (A) LMW anticancer agents (black) can distribute throughout whole normal body resulting in serious side effects. (B) Cytotoxic immunoconjugates (blue) accumulate selectively in the tumor tissue. Successful (upper) and failed (lower) immunoconjugate therapy were shown.

utilizing the specific binding ability between the antibody and antigen or between the ligand and its receptor. The passive targeting system can be achieved by the EPR effect, that is, the enhanced permeability and retention effect [1–3]. Small molecules easily leak from normal vessels in the body, which gives small molecules a short plasma half life. On the other hand, macromolecules have a long plasma half life because they are too large to pass through the normal vessel walls, unless they are trapped by the reticuloendothelial system (RES) in various organs. In the solid tumor tissues, it was found that solid tumors generally possess the several pathophysiological characteristics: hypervasculature, secretion of vascular permeability factors stimulating extravasation of macromolecules within the cancer, and absence of effective lymphatic drainage from tumors that impedes the efficient clearance of macromolecules accumulated in solid tumor tissues.

Macromolecules and lipids in the interstitial tissue are known to be recovered via the lymphatics in normal tissues [4]. The limited recovery from the lymphatic system in tumor tissues may be attributed to poor development of the lymphatics in tumor tissues, which has been demonstrated by using lipid lymphographic agents [5].

Although there is no clear anatomical proof that tumor lymphogenesis is implicated in the drainage of extravasated macromolecules in human, some studies have indicated that the growth of lymphatic vessels is actively involved in tumor dissemination [6].

This inconsistency regarding tumor lymphogenesis may be due to differences between mice and humans, or differences among tumor types. These characteristics of solid tumors are the basis of the enhanced permeability and retention effect, the EPR effect (Fig. 2). Based on the EPR effect, several formulations categorized in passive targeting have been developed and some of them such as doxil [7] and abraxane [8] have been approved in clinical use and ACAs incorporating micelles and polymer conjugated ACAs are now under preclinical and clinical evaluation [9–11].

Meanwhile, mAb is also too large to pass through the normal vessel wall but easily extravasate from leaky tumor vessels and long retained in the solid tumor tissue by utilizing the EPR effect. Moreover, mAb can target the tumor cell actively. Therefore, to date, numerous mAbs recognizing molecules on tumor cell surfaces have been developed and conjugated with ACAs, radioisotopes, or toxins to create so-called missile therapy ([12–14] and Table 1). Initially, the missile therapy strategy was expected to be highly successful.

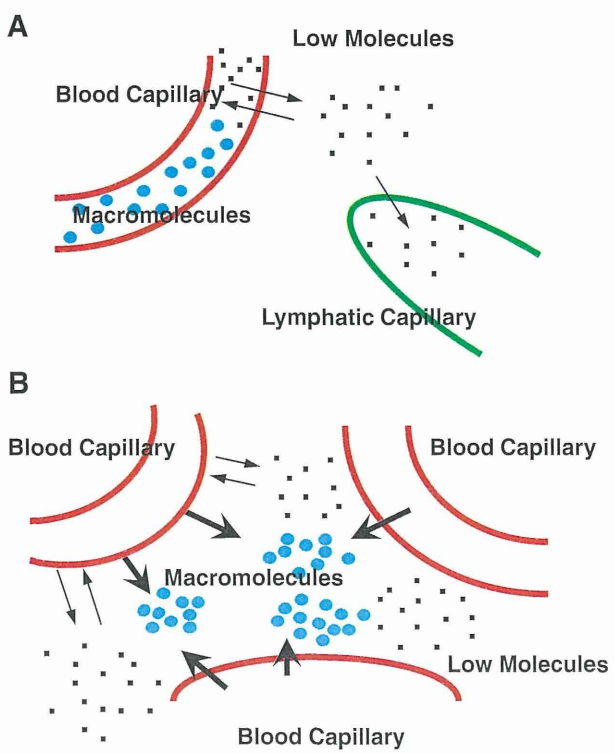

Fig. 2. Enhanced Permeability Retention (EPR) effect.Diagramatic presentation of normal tissue (A) and tumor tissue (B). In tumor (B), macromolecules are extravasated from tumor blood vessels and retained in tumor tissue for a long time because of absence of the lymphatic capillary.Low molecular substances (including a conventional anticancer drug) traverse freely between the interstitial space and the blood capillary.