# Comparative study of the antitumor activity of *Nab*-paclitaxel and intraperitoneal solvent-based paclitaxel regarding peritoneal metastasis in gastric cancer

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**Abstract.** Intraperitoneal (i.p.) chemotherapy with paclitaxel (PTX) has been shown to be a promising treatment strategy for peritoneal metastasis. The present study focused on the comparative evaluation of the therapeutic efficacy of nanoparticle albumin-bound PTX (*Nab*-PTX) and i.p. administration of the conventional solvent-based PTX (Sb-PTX). We also investigated the difference in antitumor activity depending on the route of administration in the *Nab*-PTX treatment. *Nab*-PTX was administered i.p. or intravenously (i.v.) and Sb-PTX was administered i.p. at equitoxic and equal doses to nude mice bearing gastric cancer OCUM-2MD3 cell subcutaneous and peritoneal xenografts. Therapeutic efficacy of Sb-PTX and *Nab*-PTX was evaluated as inhibition of tumor growth using a peritoneal metastatic model with subcutaneous xenografts. The survival rate was also investigated using mouse peritoneal models. For assessment of subcutaneous tumors, the change in tumor volume was measured, and for assessment of peritoneal tumors, the weight of ascitic fluid and the total peritoneal tumor burden were measured for each individual mouse. At equitoxic doses, treatment with *Nab*-PTX resulted in a greater reduction in the size of subcutaneous tumors and the weight of ascites and peritoneal burden as compared with i.p. Sb-PTX ($P<0.05$). Treatment with i.p. and i.v. *Nab*-PTX also achieved greater survival benefit than i.p. Sb-PTX ($P<0.05$). In contrast, there was no significant difference in the degree of tumor reduction and the survival time between both drugs at equal doses. With regard to the route of administration, the antitumor efficacy of *Nab*-PTX after i.v. administration was equivalent to the efficacy after i.p. administration. These results suggest that i.v. *Nab*-PTX may be another encouraging treatment option that can target peritoneal dissemination in gastric cancer.

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## Introduction

Gastric cancer is one of the major causes of cancer-related death worldwide; however, recent advances in systemic chemotherapy regimens have shown encouraging tumor response rates and increased survival in patients with unresectable or metastatic gastric cancer (1). However, treatment outcomes for patients with peritoneal metastasis, which is the most frequent metastatic pattern of recurrence, have not improved sufficiently (2).

Paclitaxel is an anticancer agent with a wide spectrum of antitumor activity in cancers that include ovarian, breast, gastric and lung (3-5). This drug stabilizes polymerized microtubules and enhances microtubule assembly, and thus arrests cells in the cell cycle in the G0/G1 and G2/M phases leading to cell death (6).

In unresectable or recurrent gastric cancer, including cases with malignant ascites, treatment with paclitaxel has achieved relatively good response rates (7-9). Intraperitoneal (i.p.) administration of paclitaxel is now attracting attention as an effective treatment for peritoneal metastasis, since a high concentration of the drug is maintained in the peritoneal cavity over a long period of time due to its high molecular weight and bulky structure (10,11). The i.p. paclitaxel regimen has been shown to prolong survival in a phase III study involving

ovarian cancer with peritoneal metastasis, and has been approved as a recommended regimen by the National Cancer Institute in the US (12). In gastric cancer, a recent phase II study of intravenous (i.v.) and i.p. paclitaxel combined with S-1 (an oral fluoropyrimidine derivative, combining tegafur with two modulators) showed a 1-year overall survival rate of 78% with a median survival time (MST) of 22.5 months for patients with peritoneal metastasis from gastric cancer (13). In addition, it has been reported that other clinical trials involving i.p. chemotherapy with taxane agents have shown favorable prognoses with an MST of 16.2-24.6 months (14-16). Therefore, a multicenter randomized clinical trial is now ongoing to generate evidence regarding i.p. chemotherapy for gastric cancer patients with peritoneal metastasis.

The conventional formulation of paclitaxel, which has poor solubility in water, requires the solubilization of the drug in a 1:1 solution of cremophor-EL (Cr-EL) and dehydrated ethanol to arrive at solvent-based PTX (Sb-PTX: Taxol®; Bristol-Myers Squibb, New York, NY, USA). Because of the large amount of Cr-EL used and the non-specific biodistribution of the drug in both tumors and normal tissues, Sb-PTX has been associated with serious side-effects, including severe hypersensitivity reactions, myelosuppression and neurotoxicity (17-19). In particular, Cr-EL has a negative impact on the efficacy of paclitaxel by forming micelles that entrap the drug in the plasma compartment (20).

Nanoparticle albumin-bound PTX (*Nab*-PTX: Abraxane®; American BioScience, Inc., Santa Monica, CA, USA) is an albumin-bound, 130-nm particle formulation of paclitaxel, which is devoid of any solvents or ethanol. *Nab*-PTX was developed to take advantage of the antitumor activity of paclitaxel while decreasing or eliminating the toxicities typically associated with Cr-EL (19,21). Thus, since *Nab*-PTX delivery is not complicated by solvents, a higher dose can be administered relative to Sb-PTX. In a pivotal phase III trial of *Nab*-PTX and Sb-PTX as first-line therapy in patients with metastatic breast cancer at the label-indicated doses, the dose of paclitaxel delivered was 49% higher for patients receiving *Nab*-PTX than Sb-PTX; this suggested that a higher dose intensity is feasible with *Nab*-PTX. In addition, albumin has the natural ability to promote drug delivery to tumors by initiating albumin receptor (gp60)-mediated transcytosis across endothelial cells (22,23), and facilitates the accumulation of drugs in tumors via binding to secreted protein acidic and rich in cysteine (SPARC) (24,25).

*Nab*-PTX and Sb-PTX have been extensively investigated in comparative clinical and experimental studies, and have exhibited unequivocal antitumor activity and minor side-effects in the treatment of breast cancer and non-small cell lung carcinoma (21,26).

In gastric cancer, second line chemotherapy with *Nab*-PTX has shown a response rate of 27.8% and a disease control rate of 59.3% in a phase II study involving patients with unresectable and metastatic gastric cancer (27). Nonetheless, little is known concerning the efficacy of *Nab*-PTX with regard to peritoneal metastasis, which is biologically more malignant and has a severe prognosis.

The aim of the present study was to investigate for the first time the antitumor effects of *Nab*-PTX as compared with i.p. Sb-PTX using a preclinical model of peritoneal metastasis. In addition, we evaluated the difference in antitumor activity between i.p. and i.v. administration of *Nab*-PTX. This was because i.p. chemotherapy, in spite of its survival advantages, is limited by the complicated procedure involved in positioning the access port and several other complications, including infection due to prolonged use of the in-dwelling catheter and local toxicity (e.g. abdominal pain and other gastrointestinal toxicities). For these purposes, we used four treatment groups in the present study: control group; i.p. Sb-PTX-treated group; i.p. *Nab*-PTX-treated group; and i.v. *Nab*-PTX-treated group. Antitumor activity was compared among these four groups at equitoxic and equal doses in nude mice bearing OCUM-2MD3 subcutaneous and peritoneal xenografts.

## Materials and methods

*Study drugs*. *Nab*-PTX (ABI-007, Abraxane®; American BioScience) and Sb-PTX (Taxol®; Bristol-Myers Squibb) was purchased from a hospital pharmacy. Both drugs were reconstituted in normal saline, prepared fresh daily as required, and administered within 1 h of preparation.

*Cell lines and cell culture*. OCUM-2MD3, a high peritoneal-seeding cell line from human scirrhous gastric cancer, was kindly provided by the Department of Surgical Oncology of Osaka City University of Medicine (28). These cells were cultured in 10 ml of medium at 37˚C in a humidified atmosphere of 5% $CO_2$ in air. OCUM-2MD3 cells were grown in Dulbecco's modified Eagle's medium (DMEM) (Life Technologies, Tokyo, Japan) supplemented with 10% heat-inactivated fetal bovine serum, 100 IU/ml penicillin, 100 mg/ml streptomycin, 2 mM glutamine and 0.5 mM sodium pyruvate. Cells were grown to confluency and harvested by trypsinization with 0.25 mg/ml trypsin/EDTA (Life Technologies) and suspended in culture medium before use.

*Animals and development of the gastric cancer model*. Female athymic NCr-nu nude mice (4-6 weeks of age) were purchased from Charles River Laboratories (Yokohama, Japan). All animal experiments were performed in accordance with the guidelines of the Institutional Animal Care and Use Committee of Kanazawa University. They were housed in specific pathogen-free conditions and fed standard chow pellets and water *ad libitum*. At the start of the treatment, body weights ranged from 21 to 25 g and ages ranged from 6 to 8 weeks. To evaluate systemic and intraperitoneal antitumor activity, the mice were inoculated simultaneously with $1x10^7$ OCUM-2MD3 cells suspended in 1 ml PBS intraperitoneally and $2x10^6$ OCUM-2MD3 cells suspended in 200 $\mu$l PBS subcutaneously in the flank.

Mice for examination of the survival rate were inoculated with $1x10^7$ OCUM-2MD3 cells intraperitoneally as a peritoneal metastatic model.

*Evaluation of antitumor activity*

*Treatment schedule*. After tumor inoculation (day 0) the mice were randomly divided into four groups, each consisting of five animals that received different treatments: control group; i.p. Sb-PTX-treated group; i.p. *Nab*-PTX-treated group; and i.v. *Nab*-PTX-treated group.

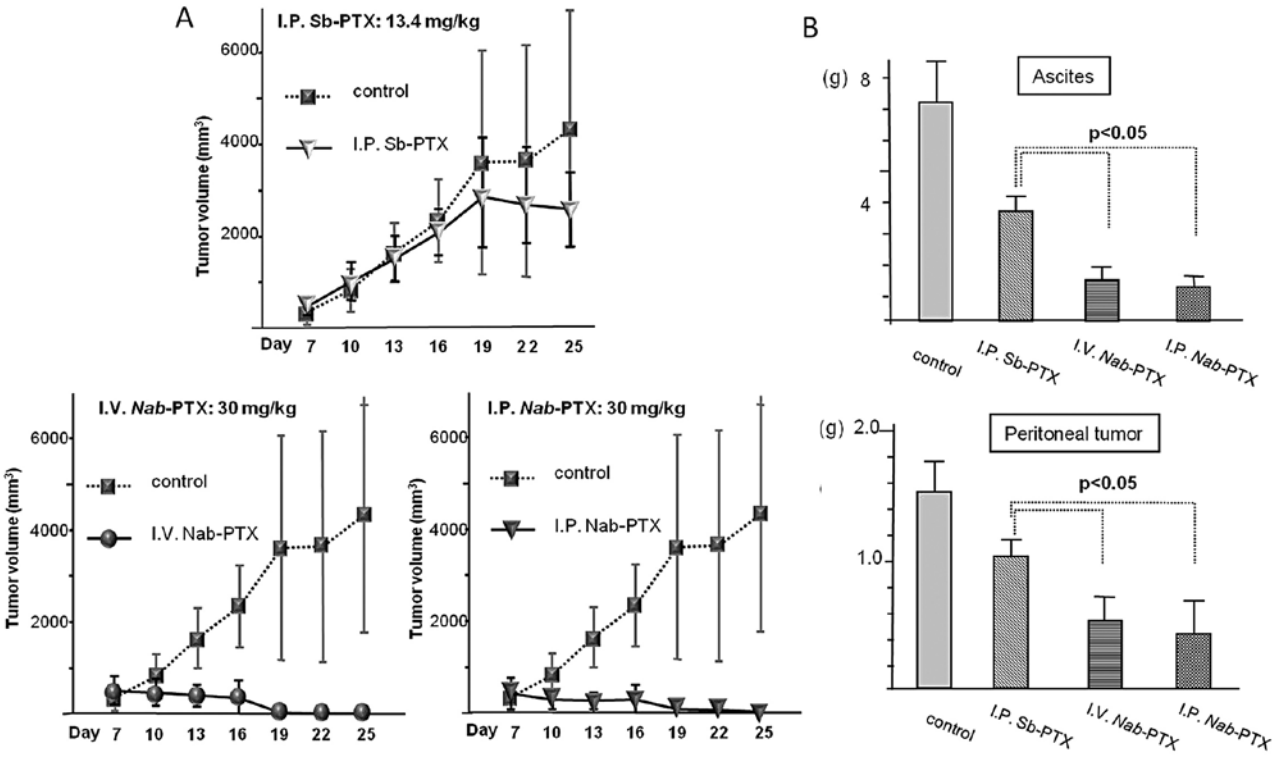


Figure 1. Antitumor activity at equitoxic doses. (A) Antitumor activity of Sb-PTX and *Nab*-PTX regarding subcutaneous tumors at equitoxic doses. Subcutaneous tumor volumes in mice treated with equitoxic doses of i.p. Sb-PTX (13.4 mg/kg/day) or i.p. *Nab*-PTX (30 mg/kg/day) or i.v. *Nab*-PTX (30 mg/kg/day) were compared with the untreated controls (mean ± SE; n=5). Both *Nab*-PTX-treated groups showed greater tumor reduction than the i.p. Sb-PTX-treated group (P<0.01). (B) Antitumor activity of Sb-PTX and *Nab*-PTX regarding peritoneal tumors at equitoxic doses. The weights of ascites and peritoneal tumors treated with equitoxic doses of i.p. Sb-PTX, i.p. *Nab*-PTX, or i.v. *Nab*-PTX at 28 days after intraperitoneal inoculation of OCUM-2MD3 cells were compared with the untreated controls (mean ± SE; n=5). Both *Nab*-PTX-treated groups also showed significantly greater antitumor activity than the i.p. Sb-PTX-treated group in terms of the weights of ascites and peritoneal tumors (P<0.05).

In the control and i.p. treatment groups, phosphate-buffered saline or the PTX formulations were given i.p., and the injection volume was 1 ml/mouse to optimize spreading of the drugs throughout the entire peritoneal cavity. In the i.v. treatment group, *Nab*-PTX was injected into the tail vein, and the injection volume was 100 $\mu$l/mouse. These four groups were used in each evaluation as described below.

Drug treatment was initiated on day 7, and each drug was administered once daily for 7 consecutive days. Sb-PTX and *Nab*-PTX were administered at equitoxic doses (MTDs: 13.4 and 30 mg PTX/kg/day, respectively) that were previously reported in a mouse study (29) and at an equal dose (10 mg PTX/kg/day).

*Assessment of tumor response to Nab-PTX and Sb-PTX.* Therapeutic efficacy of Sb-PTX and *Nab*-PTX was evaluated as inhibition of tumor growth using a peritoneal metastatic model with subcutaneous xenografts at equitoxic and equal doses. Each group consisted of five mice with respect to each treatment.

For subcutaneous tumors, the size was measured with a digital caliper twice weekly. Tumor growth was calculated using the formula (L x $W^2$)/2, where L is the longest and W is the shortest tumor diameter.

For assessment of peritoneal metastasis, the mice were sacrificed using isoflurane inhalation and necropsied on day 25, and samples of ascites and peritoneal nodules were collected. The weight of ascitic fluid and the total peritoneal tumor burden were measured for each individual mouse.

In addition, the survival time with respect to each treatment was evaluated in the peritoneal metastatic models. The mice were euthanized when they became moribund (the day of death being considered the limit of survival).

*Statistical analyses.* Statistical analyses were carried out using the computer software package SPSS 10.0. Statistical differences for two groups were evaluated using the Student's t-test, and one-way ANOVA for multiple groups. Survival rates were expressed using Kaplan-Meier curves and their comparison was analyzed using the log-rank test. A value of P<0.05 was considered to indicate a statistically significant result.

## Results

*Antitumor activity of Sb-PTX and Nab-PTX at equitoxic doses.* The antitumor effects of i.p. Sb-PTX, i.p. *Nab*-PTX, and i.v. *Nab*-PTX were evaluated at equitoxic doses in the subcutaneous and intraperitoneal OCUM-2MD3 xenograft models.

Regarding the subcutaneous tumors, the *Nab*-PTX-treated group showed greater antitumor activity than that of the i.p. Sb-PTX-treated group (P<0.01). Complete regression was observed in both the i.p. and i.v. *Nab*-PTX-treated groups. There was no significant difference in the measurement of the

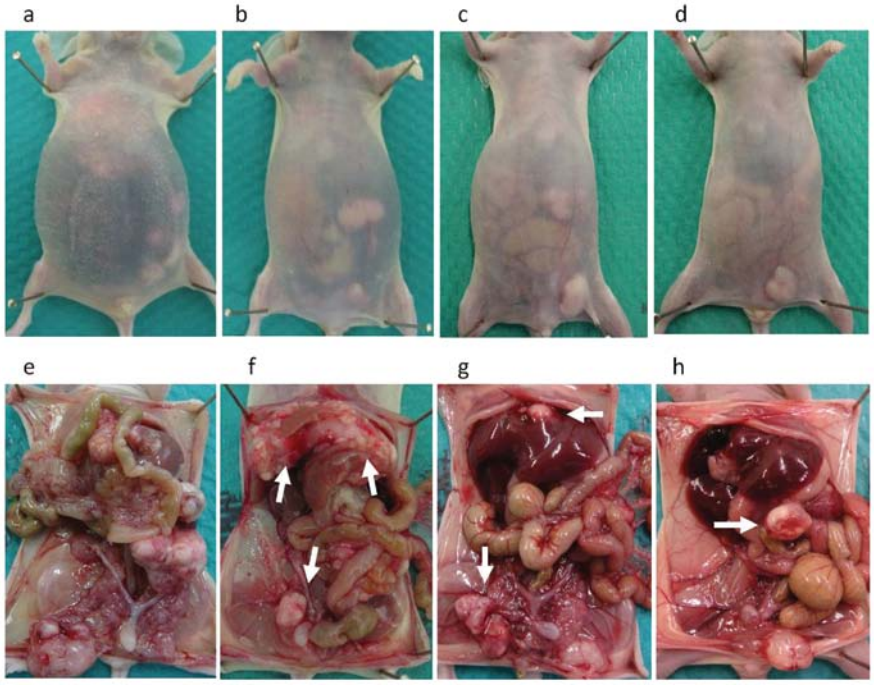


Figure 2. Representative images of the peritoneal metastatic models. Representative images of the accumulation of ascites and peritoneal tumors at the time of death in (a and e) the control group, (b and f) the group treated with i.p. Sb-PTX, (c and g) the group treated with i.v. *Nab*-PTX and (d and h) the group treated with i.p. *Nab*-PTX. In the control group, massive ascites and multiple tumors were extensively noted in the peritoneal cavity, whereas the accumulation of ascites and peritoneal tumors (white arrow) was reduced in the treatment groups.

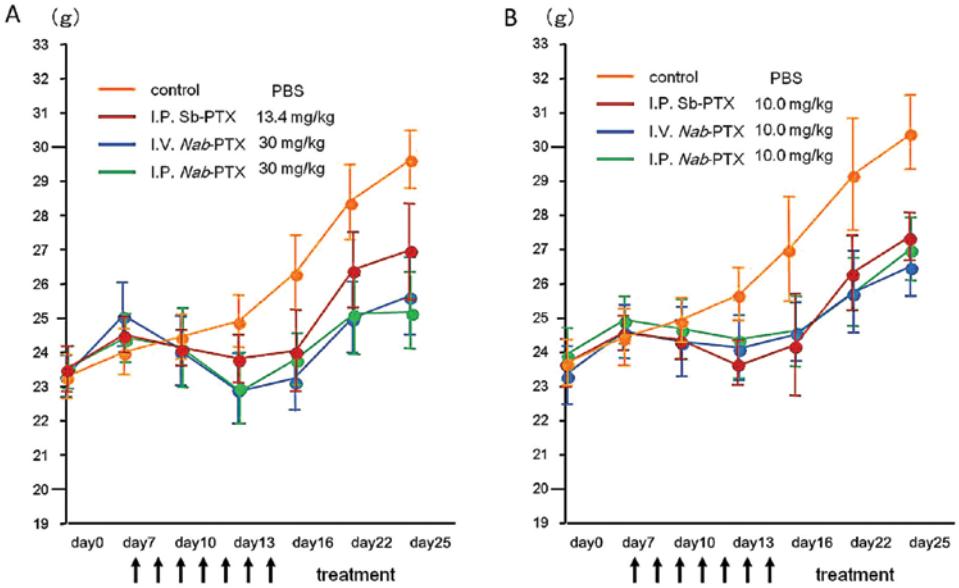


Figure 3. Body weight changes following intravenous or intraperitoneal treatment of the different paclitaxel formulations. (A) Body weight changes in the subcutaneous and peritoneal metastatic models in the equitoxic dose study. (B) Body weight changes in the equal dose study. Mean body weights were not significantly different among the i.p. Sb-PTX-treated group, the i.v. *Nab*-PTX-treated group and the i.p. *Nab*-PTX-treated group at both doses. Data represent the mean ± SE of 5 mice per group.

subcutaneous tumor volume between the routes of administration (i.v./i.p.) following treatment with *Nab*-PTX (Fig. 1A).

Following assessment of the peritoneal metastasis, complete regression was not observed in either the *Nab*-PTX or Sb-PTX-treated group (Fig. 1B). As compared with the control group, all treatment groups displayed significantly slower growth of peritoneal tumors and relief from the accumulation of ascites. Representative images in the four groups are shown in Fig. 2. Among the treatment groups, both the i.p. and i.v. *Nab*-PTX-treated groups displayed significant tumor reduction relative to the i.p. Sb-PTX-treated group ($P<0.05$). With regard to the accumulation of ascites, both *Nab*-PTX-treated groups also showed significantly greater antitumor activity than the i.p. Sb-PTX-treated group ($P<0.05$). In the *Nab*-PTX-treated groups, there was no significant difference in the weights of ascites and the peritoneal tumors between

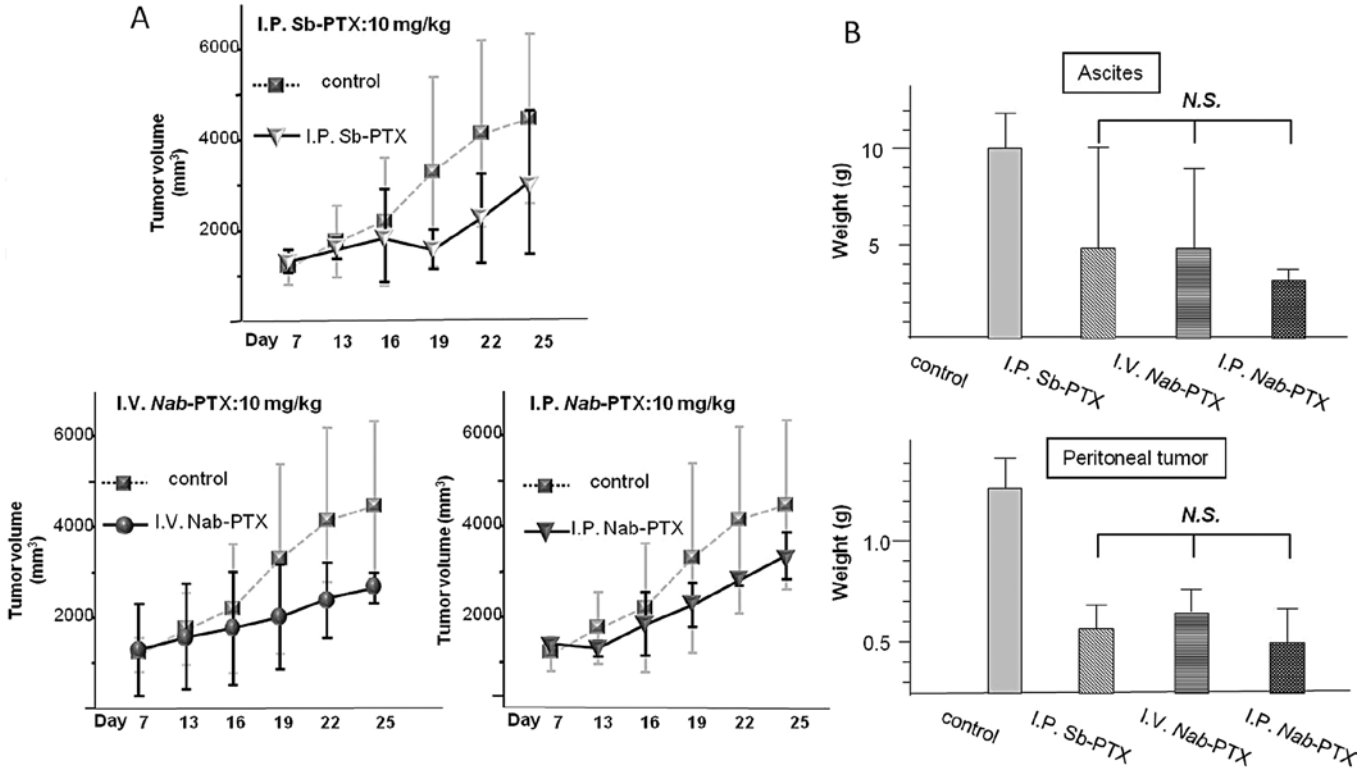


Figure 4. Antitumor activity at equal doses. (A) Antitumor activity of Sb-PTX and *Nab*-PTX regarding subcutaneous tumors at an equal dose. Subcutaneous tumor volumes in mice treated with an equal dose (10 mg/kg/day) of i.p. Sb-PTX, i.p. *Nab*-PTX or i.v. *Nab*-PTX were compared with the untreated controls (mean ± SE; n=5). No significant reduction in tumor size was observed among the three treatment groups. (B) Antitumor activity of Sb-PTX and *Nab*-PTX regarding peritoneal tumors at an equal dose. The weights of ascites and peritoneal tumors in mice treated with an equal dose of i.p. Sb-PTX, i.p. *Nab*-PTX or i.v. *Nab*-PTX at 28 days after i.p. inoculation of OCUM-2MD3 cells (mean ± SE; n=5). There were no significant differences between the three treatment groups.

the i.p. and i.v. administration routes. All treatment sequences were well tolerated, and mean body weights were not significantly different among the three treatment groups (Fig. 3A). The body weight in the control group was significantly higher than the body weight in all of the treatment groups (P<0.05). This was mainly due to the accumulation of ascites and peritoneal tumors.

*Antitumor activity of PTX and Nab-PTX in the subcutaneous tumors administered at an equal dose*. The antitumor effects of the two PTX formulations were investigated at an equal dose (10.0 mg/kg/day for Sb-PTX and *Nab*-PTX, concurrently) in the same manner as the equitoxic study. As shown in Fig. 4A, the volume of the subcutaneous tumors was significantly reduced in all of the treatment groups relative to the control group (P<0.01), whereas no significant reduction in tumor volume was observed when comparing the three treatment groups.

In the assessment of peritoneal metastasis, the weights of ascites and the peritoneal tumors were significantly reduced in all treatment groups relative to the control group (P<0.01). However, there was no significant difference among the three treatment groups (Fig. 4B).

All treatment sequences were well tolerated, and mean body weights were not significantly different among the three treatment groups as well as in the equitoxic dose study (Fig. 3B).

*Survival rate*. The survival rate in the peritoneal metastatic model was also evaluated using Kaplan-Meyer survival curves at equitoxic and equal doses (Fig. 5). All five mice in the control group developed ascites and died within 19-32 days after tumor cell inoculation; the median survival time was 25 days. At equitoxic doses, the median survival time was 96 days for the i.p. Sb-PTX-treated group, 122 days for the i.v. *Nab*-PTX-treated group and 126 days for the i.p. *Nab*-PTX-treated group. The survival benefit was greater in the i.p. and i.v. *Nab*-PTX-treated groups than that in the i.p. Sb-PTX-treated group (P=0.034 and P=0.047, respectively). Regarding the route of drug delivery, i.p. administration resulted in no significant improvement in survival when compared with i.v. administration in the *Nab*-PTX treated groups. In addition, there was no significant difference in relation to survival time among the treated groups at an equal dose.

## Discussion

The primary aims of the present study were to clarify whether or not *Nab*-PTX had any advantages over i.p. Sb-PTX in the treatment of peritoneal metastasis from gastric cancer, and to evaluate potential differences in the antitumor activity of *Nab*-PTX between i.v. and i.p. administration routes. *Nab*-PTX demonstrated significantly greater antitumor efficacy in both peritoneal and subcutaneous tumors as compared with i.p. Sb-PTX at equitoxic doses (*Nab*-PTX, 30 mg/kg/day; Sb-PTX,

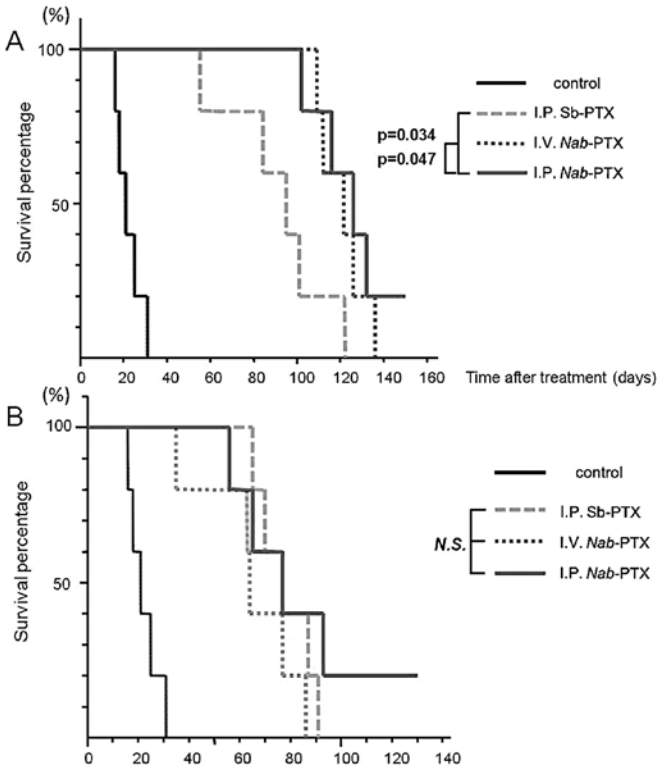


Figure 5. Therapeutic efficacy of Sb-PTX and *Nab*-PTX in regards to the survival rate (Kaplan-Meier curves) at equitoxic and equal doses. Drug treatment was initiated on day 7 after inoculation, and each drug was administered once daily for 7 consecutive days (each group, n=5). (A) The mice in the treatment groups received equitoxic doses of i.p. Sb-PTX (13.4 mg/kg/day), i.p. *Nab*-PTX (30 mg/kg/day) or i.v. *Nab*-PTX (30 mg/kg/day). Significant improvement in survival in the i.p. and i.v. *Nab*-PTX-treated groups was observed relative to the i.p. Sb-PTX-treated group (P=0.034 and P=0.047, respectively). (B) The mice in the treatment groups received an equal dose (10 mg/kg/day) of i.p. Sb-PTX, i.p. *Nab*-PTX or i.v. *Nab*-PTX. There was no significant difference with regard to survival time between the treated groups receiving an equal dose.

13.4 mg/kg/day) using a mouse model. In survival studies, a significant improvement in survival time was observed in the *Nab*-PTX-treated groups relative to the i.p. Sb-PTX-treated group under the same conditions.

Additional studies involving other tumor models and *in vivo* mechanism-related studies have confirmed the high accumulation characteristics of *Na*b-PTX (24,25,29,32). It is generally considered that the free or unbound form of the drug is the active fraction, since drug bound to proteins or other macromolecules may be unable to cross cell membranes (30). In clinical studies, Sb-PTX has been shown to be highly bound to protein in plasma, with Cre-EL further decreasing the free/unbound fraction of the drug (30,31). The advantage of *Nab*-PTX is its water solubility, achieved without the use of Cre-EL and ethanol. Indeed, Gardner *et al* (32) reported that the formulation of *Nab*-PTX allowed a much higher fraction of unbound paclitaxel than that of Sb-PTX, and that the maximal concentration of unbound paclitaxel was ~10-fold higher for *Nab*-PTX in their pharmacokinetic study.

An additional advantage of *Nab*-PTX is its albumin-bound particle formulation. Albumin is assumed to be a ubiquitous carrier of biomolecules in human blood, which accumulate in tumors by means of a receptor-mediated transport mechanism; this involves an albumin-specific receptor such as glycoprotein 60, or the permeation and retention effect (22,23).

Another molecular mechanism proposed to play a potential role in the accumulation of *Nab*-PTX in tumors involves albumin-binding proteins such as SPARC in proximity to tumors (24). Clinical data suggest a correlation between tumoral SPARC expression and the positive clinical outcome of patients treated with *Nab*-PTX (24,25). Indeed, SPARC expression has been confirmed in both gastric cancer tissues and the microenvironment of peritoneal metastasis (33-35). Accordingly, it has been hypothesized that *Nab*-PTX may take advantage of each of these mechanisms to reach the microenvironment of the tumor.

For these reasons, we initially hypothesized that *Nab*-PTX would show greater antitumor effects than Sb-PTX, even at an equal dose (10 mg/kg/day). However, in the present study, the equal dose comparison did not indicate a significant difference between *Nab*-PTX and Sb-PTX in terms of the shrinkage of subcutaneous and peritoneal tumors. In addition, *Nab*-PTX did not increase the median survival time as compared with Sb-PTX at an equal dose. This finding indicates that the greater antitumor activity of *Nab*-PTX was mainly attributable to a higher-dose administration relative to Sb-PTX. We could not clarify the reason why the higher tumor accumulation of *Nab*-PTX relative to Sb-PTX did not reflect antitumor efficacy in our study. However, we consider the comparison of equitoxic doses to be more clinically applicable rather than comparison at an equal dose, since chemotherapy is generally administered at the highest tolerated dose. Indeed, these findings are supported by a recent phase III clinical study, which showed significantly higher therapeutic efficacy using *Nab*-PTX as compared with Sb-PTX at equitoxic doses (21).

One of the limitations of the present study was the inadequacy to evaluate the toxicity of both drugs. Although we measured the body weight of mice during the course of treatment, blood examination for neutropenia, liver or renal dysfunctions was not performed. Because body weight is critically affected by tumor burden, ascites and cachexia, further investigation is required to validate the side-effects of *Nab*-PTX.

Regarding the route of administration, there was no significant difference between i.p. and i.v. administration of *Nab*-PTX in any of the parameters evaluated, such as volume change in the subcutaneous tumors, the weight of ascites and peritoneal tumors and survival times of the mice. Although the effects of i.v. *Nab*-PTX have been reported in several studies, the effects of this nanoparticulate paclitaxel following i.p. administration remain unclear.

Intraperitoneal Sb-PTX was expected to demonstrate high efficacy for peritoneal metastasis, since Sb-PTX is retained for long periods in the peritoneal cavity after i.p. administration due to its large molecular weight and fat solubility (36). However, two shortcomings are that the drug infiltrates only the surface of the peritoneal tumor and that the drug is not fully absorbed into the systemic circulation.

On the other hand, our results suggest that *Nab*-PTX following i.v. administration may infiltrate into the peritoneal tumor to the same degree as i.p. injection. Conversely,

*Nab*-PTX administered intraperitoneally might be absorbed into the systemic circulation more easily than Sb-PTX.

We speculate that one of the reasons for these findings is that *Nab*-PTX is unaffected by the ability of Cre-EL to inhibit transport into the bloodstream and binding to endothelial cells around the tumor. In addition, the enhanced permeability and retention (EPR) effect, which is known as selective accumulation of nanoparticle drugs by passive targeting is thought to be another reason (37). Through the EPR effect, nanoparticle drugs are retained for a long period in the systemic circulation, are easily extravasated from tumor vessels into the interstitium of tumor tissue, and accumulate there for longer periods than conventional small-molecule agents (38-40). On the basis of these findings, i.v. administration is considered to be a more feasible and simplified treatment than i.p. administration for *Nab*-PTX. This is because i.p. chemotherapy requires surgical intervention to position the access port and has several complications and local toxicities. In the next stage of evaluation, we will investigate the paclitaxel concentrations in plasma and ascites after i.v. administration of *Nab*-PTX in patients with ascites due to peritoneal metastasis resulting from gastric cancer.

In conclusion, we demonstrated, using a peritoneal metastatic model of gastric cancer, that *Nab*-PTX showed greater efficacy than i.p. Sb-PTX at equitoxic doses involving a subcutaneous xenograft model. The antitumor efficacy of *Nab*-PTX regarding peritoneal metastasis after i.v. administration was equivalent to i.p. administration. Although further studies are necessary for a more detailed evaluation, i.v. *Nab*-PTX treatment might be another encouraging option for targeting not only peritoneal metastasis, but also primary sites or other metastatic sites. The present preclinical study suggests the need for a clinical study to evaluate the antitumor effects of *Nab*-PTX in gastric cancer patients with peritoneal metastasis.

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