



Metronomic oral paclitaxel shows anti-tumor effects in an orthotopic mouse model of ovarian cancer

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Objective: The purpose of this study was to compare the *in vivo* anti-tumor efficacy of a mucoadhesive, lipid-based, oral paclitaxel formulation (DHP107) with traditional, intraperitoneal (IP) paclitaxel using an orthotopic mouse model of chemotherapy-sensitive SKOV3ip1 ovarian cancer.

Methods: To determine the optimal therapeutic dose of oral paclitaxel, DHP107 was administered per os to female athymic nude mice at 0, 25, or 50 mg/kg twice per week. Control mice received 100 μ L saline once per week. IP injections of paclitaxel at 5 mg/kg once per week were used for comparison. To evaluate the potential therapeutic effect of metronomic DHP107 chemotherapy, mice received DHP107 50 mg/kg once per week per os, which was compared with 25 mg/kg twice per week and with vehicle-treated controls.

Results: Low-dose DHP107 (25 mg/kg) twice per week was as effective as IP paclitaxel (5 mg/kg once a week) but high-dose DHP107 (50 mg/kg once per week) was less effective at inhibiting tumor growth in an orthotopic mouse model (88%, 82%, and 36% decrease in tumor weight, respectively). Mice that received 25 mg/kg DHP107 twice per week or 50 mg/kg DHP107 once per week per os had a significant decrease in tumor weight compared with vehicle-treated controls ($p < 0.01$, both doses).

Conclusion: Metronomic oral chemotherapy with DHP107 showed anti-tumor efficacy *in vivo* similar to IP paclitaxel in an orthotopic mouse model.

Keywords: Chemotherapy, DHP107, Oral paclitaxel, Ovarian cancer

INTRODUCTION

Ovarian cancer remains the most common cause of death due to gynecologic malignancy. Cytoreductive surgery followed by intermittent chemotherapy with taxane and platinum-based chemotherapeutic agents is the standard

treatment for ovarian cancer [1-3]. Paclitaxel is a very effective anticancer drug for cancers such as ovarian, breast, gastric, and non-small-cell lung cancer [4-7]. Taxol is the most widely marketed form of paclitaxel and is administered as a 3-hour infusion every 3 weeks with premedication to prevent severe hypersensitivity reactions, so the patient must be hospitalized. Because paclitaxel is poorly soluble in water, the commercial intravenous formulation contains a polyoxyethylated castor oil, Cremophor EL (BASF Co., Ludwigshafen, Germany), which acts as a pharmaceutical solvent to stabilize the emulsion of nonpolar paclitaxel in aqueous systems [8,9].

The development of an oral form of paclitaxel would prevent unnecessary hospitalization and hypersensitivity reactions. Furthermore, oral administration facilitates metronomic

Received Jul 25, 2013, Revised Nov 13, 2013, Accepted Dec 5, 2013

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therapy. Advantages of continuous exposure to paclitaxel have been reported. Weekly paclitaxel administration improved outcomes compared with administration every third week [10]. Continuous exposure to low concentrations of paclitaxel has been reported to have anti-tumor activity by inhibiting tumor-associated angiogenesis [11,12]. However, per os administration of paclitaxel may decrease bioavailability due to P-glycoprotein (P-gp) overexpression [13]. In an attempt to make oral paclitaxel formulations safer, a clinical, mucoadhesive, lipid-based, oral paclitaxel formulation (DHP107) has recently been developed. The formulation comprises edible lipids and a Food and Drug Administration-approved emulsifier and does not include toxic excipients. In previous publications, oral administration of DHP107 enhanced paclitaxel absorption and tissue distribution [14-16].

This study aimed to compare the anti-tumor efficacy of metronomic DHP107 with that of traditional intraperitoneal (IP) paclitaxel *in vivo* using an orthotopic mouse model of chemotherapy-sensitive SKOV3ip1 ovarian cancer.

MATERIALS AND METHODS

1. Cell culture and orthotopic model of ovarian cancer

The human ovarian carcinoma cell line, SKOV3ip1, was provided by Dr Anil K. Sood (MD Anderson Cancer Center). SKOV3ip1 was maintained in RPMI-1640 supplemented with 10% fetal bovine serum (Hyclone, Logan, UT, USA) and 50 µg/mL gentamycin sulfate (Sigma-Aldrich, St Louis, MO, USA).

Eight-week-old female, athymic nude mice (NCR-nu) were purchased from Orient Bio, Inc. (Seoul, Korea) and maintained for 1 week. All mice were cared for according to institutional guidelines following the American Association for Accreditation of Laboratory Animal Care protocols. All studies were approved and supervised by the Hanyang University Institutional Animal Care and Use Committee (IACUC). The mice were maintained under specific pathogen-free environmental conditions. Before cell line injection, ovarian cancer cells were washed twice with phosphate-buffered saline, detached with 0.1% cold ethylenediaminetetraacetic acid, harvested by centrifugation, and resuspended in Hank's balanced salt solution (HBSS; Invitrogen, Carlsbad, CA, USA). Cell viabilities were determined by trypan blue exclusion. A suspension of 1.0×10^6 cells/100 µL was injected IP into the mice. The experiment was performed in two parts: the first part was to determine the optimal therapeutic doses of paclitaxel (Padexol, Shinpung Pharmaceuticals, Seoul, Korea) and DHP107 (Daewha Pharmaceutical Co., Hoengseong, Korea); and the second part was to compare the therapeutic efficacies of

paclitaxel and DHP107. The experimental drugs were donated by the pharmaceutical companies.

To determine the optimal therapeutic dose of paclitaxel, mice (10 per treatment group) were randomly assigned to receive 1 of 4 treatments: (1) 100 µL saline once weekly (control group); (2) 100 µL of 1 mg/kg paclitaxel once weekly; (3) 100 µL of 2.5 mg/kg paclitaxel once weekly; or (4) 100 µL of 5 mg/kg paclitaxel once weekly. All treatments were administered IP 1 week after the tumor cell injections. To determine the optimal therapeutic dose of DHP107, mice (10 per treatment group) were randomly assigned to receive 1 of 4 treatments: (1) 100 µL saline once weekly (control group); (2) 100 µL of 5 mg/kg paclitaxel once weekly; (3) 100 µL of 25 mg/kg DHP107 twice weekly; or (4) 100 µL of 50 mg/kg DHP107 twice weekly.

Paclitaxel was administered IP; DHP107 and saline were administered with a blunt needle into the stomach via the esophagus.

To evaluate the efficacy of metronomic DHP107, a total dose of 50 mg/kg DHP107 weekly was administered either as 25 mg/kg DHP107 twice weekly or 50 mg/kg DHP107 once weekly. Mice (10 per treatment group) were randomly assigned to receive one of four treatments: (1) 100 µL saline once weekly (control group); (2) 100 µL of 5 mg/kg paclitaxel once weekly IP; (3) 100 µL of 50 mg/kg DHP107 once weekly per os; or (4) 100 µL of 25 mg/kg DHP107 twice weekly per os.

Treatments were continued until control mice became moribund due to the tumor burden (generally 7 weeks). All mice were killed and necropsied. The pattern and extent of abdominal disease (body weight, tumor weight, and number of tumor nodules) and pathologic effects of main organs were recorded.

2. Statistical analysis

All values are expressed as mean ± SD. For animal experiments, 10 mice were assigned to each treatment group. Mouse body weight, tumor weight, and the number of tumor nodules for each group were compared using ANOVA and $p < 0.05$ was considered significant. Statistical analyses were performed using SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Determination of the therapeutic dose of IP paclitaxel

Female athymic nude mice were injected with paclitaxel IP at doses of 1, 2.5, and 5 mg/kg once per week to determine the therapeutic dose. Saline IP injections were used as a control. The body weights of the control and experimental groups did not change significantly during the study (**Fig. 1A**).

Tumor weights decreased significantly in mice receiving 2.5 mg/kg ($p < 0.01$) and 5 mg/kg ($p < 0.01$) paclitaxel compared with those in the control group (**Fig. 1B**). The tumor weight decreased by 60% in mice receiving 1 mg/kg paclitaxel compared with that in the control group, but the difference was not statistically significant. The number of tumor nodules decreased significantly in all treated groups compared with that in the control group ($p < 0.05$) (**Fig. 1C**). The paclitaxel dose selected as a control for the therapeutic effect of DHP107 was 5 mg/kg IP once a week based on our previous study [17].

2. Determination of the therapeutic dose of DHP107

To determine the optimal therapeutic dose, female athymic nude mice received 0, 25, or 50 mg/kg DHP107 twice per week orally. Paclitaxel IP injections at 5 mg/kg weekly were used for comparison. DHP107 doses 10–20 times higher than the conventional IP paclitaxel dose was used because the bioavailability of DHP 107 is 2%–4.6% that of intravenous paclitaxel [16]. Further, we previously reported that the

inhibitory effect of DHP107 on mammary tumors at 50 mg/kg per os was equivalent to Taxol at 10 mg/kg [16]. The body weights of the control and treated groups did not change significantly during the study (**Fig. 2A**). Mice treated with DHP107 per os at 25 mg/kg ($p < 0.01$) and 50 mg/kg ($p < 0.01$) and paclitaxel IP ($p < 0.01$) showed significant decreases in tumor weight relative to vehicle-treated controls (0.44 ± 0.49 g, 0.00 ± 0.00 g, 0.02 ± 0.03 g, and 1.02 ± 0.58 g, respectively). Tumor weight decreased by half in mice that received 25 mg/kg DHP107 per os relative to control mice. Mice that received 50 mg/kg DHP107 per os twice weekly had no tumor except for 1 mouse with 1 small tumor nodule (**Fig. 2B**). The number of nodules decreased significantly in all groups treated with DHP107 per os at 25 mg/kg and 50 mg/kg, and paclitaxel IP compared with that in the controls (4.0 ± 3.3 , 0.3 ± 1.0 , 1.0 ± 0.9 , and 13.8 ± 7.3 , respectively; all $p < 0.02$). DHP107 at 25 mg/kg reduced the number of nodules to <40% (**Fig. 2C**). The tumor weight decreased and the tumor nodules disappeared almost completely at 50 mg/kg DHP107 twice per week (mean

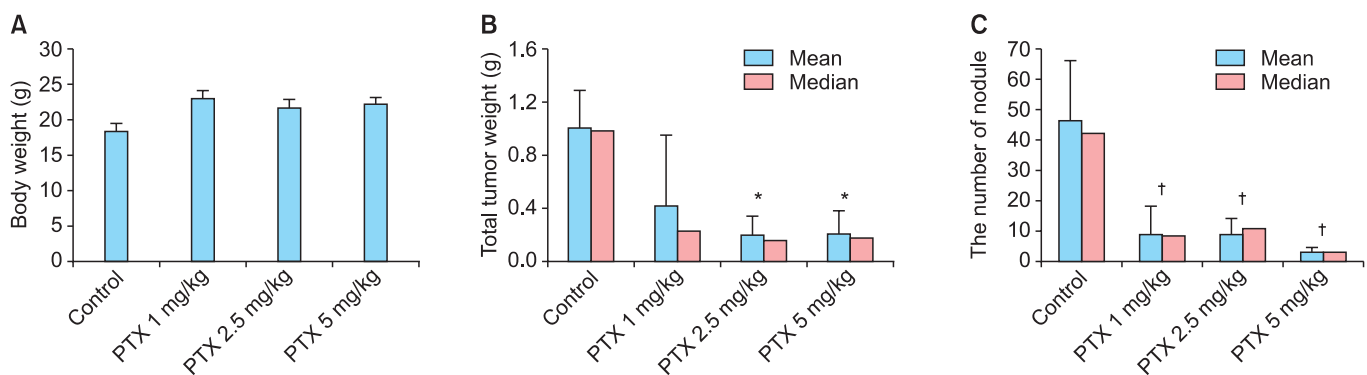


Fig. 1. Paclitaxel (PTX) was injected intraperitoneal (IP) at doses of 1, 2.5, or 5 once per week into female athymic nude mice to determine the optimal therapeutic dose of IP PTX. Saline IP injections were used as control. (A) Body weight. (B) Tumor weight (* $p < 0.01$). (C) Number of tumor nodules ($^{\dagger}p < 0.05$).

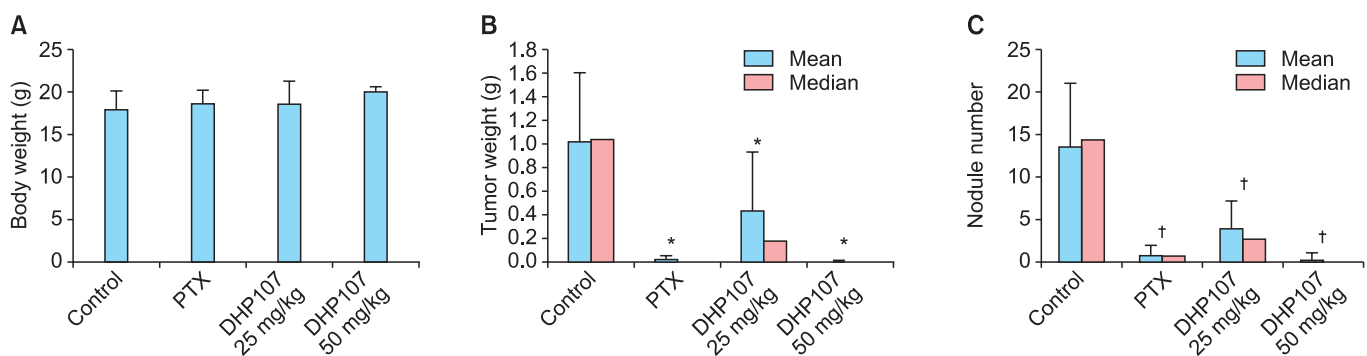


Fig. 2. DHP107 was administered per os at 0, 25, or 50 mg/kg twice per week in female athymic nude mice to determine the optimal therapeutic dose of DHP107. Paclitaxel (PTX) intraperitoneal injections at 5 mg/kg were used for comparison. (A) Body weight. (B) Tumor weight (* $p < 0.01$). (C) Number of tumor nodules ($^{\dagger}p < 0.02$).

tumor weight, 0.00 ± 0.00 g; mean number of tumors, 0.3 ± 1.0). We thought that the total dose of 100 mg/kg DHP107 once per week would also inhibit tumor weight and eliminate tumor nodules. If this is the case, we cannot compare the efficacy of metronomic chemotherapy between 50 mg/kg DHP107 twice per week and 100 mg/kg DHP107 once a week. Therefore 25 mg/kg DHP107 twice per week was selected to evaluate the efficacy of metronomic chemotherapy because it showed a statistically significant inhibition of tumor growth (57% decrease in tumor weight) and we thought that a total dose of 50 mg/kg DHP107 once a week would reduce tumor weight below or above this measurable range.

3. Evaluation of the therapeutic effect of DHP107 metronomic chemotherapy

To evaluate the potential effect of metronomic DHP107 chemotherapy, mice were treated with 0 or 50 mg/kg once a week or 25 mg/kg DHP107 twice per week per os. The body weights of the mice in the control and treated groups did not change significantly (Fig. 3A). Mice treated with low-dose DHP107 (25 mg/kg) administered twice per week and IP paclitaxel (5 mg/kg) once per week showed a significant decrease in tumor weight (all $p < 0.01$) compared with control mice (0.03 ± 0.07 g, 0.05 ± 0.09 g, and 0.28 ± 0.28 g, respectively). Metronomic DHP107 25 mg/kg twice weekly resulted in a greater decrease in tumor weight and number of tumor nodules than high-dose DHP107 50 mg/kg once a week, although the difference was not statistically significant (both $p = 0.09$) (Fig. 3B, C). Mice that were administered DHP107 50 mg/kg once a week showed some decrease in tumor weight ($p = 0.24$), but the difference was not significant compared with the control group (0.18 ± 0.25 g) (Fig. 3B). The number of nodules decreased significantly in groups treated with DHP107 per os at 25 mg/kg and paclitaxel IP compared with that in the

control group (0.8 ± 1.5 , 0.6 ± 1.2 , and 3.6 ± 1.9 , respectively; all $p < 0.01$). Mice receiving 50 mg/kg DHP107 showed some reduction in the number of nodules but the difference was not significant compared with the control group (2.3 ± 2.9 ; $p = 0.13$) (Fig. 3C).

4. Evaluation of the adverse effects of DHP107 metronomic chemotherapy on other organs

To investigate the toxicity of DHP107 after a 7-week administration to female nude mice, we collected the main abdominal and thoracic organs and sent them for pathological analysis. The stomach, small intestine, large intestine, pancreas, liver, kidneys, lungs, heart, spleen, uterus, oviducts, and ovaries were evaluated for the adverse effects of chemotherapy. There were no treatment-related findings attributable to DHP107 or paclitaxel. All adverse findings were considered incidental or agonal changes unrelated to the treatment.

DISCUSSION

In the present study, we compared the *in vivo* anti-tumor efficacy of metronomic DHP107, a novel oral form of paclitaxel administered without Cremophor EL or a concomitant P-gp inhibitor, with traditional IP paclitaxel using an orthotopic mouse model of ovarian cancer. Mice treated with low-dose metronomic DHP107 at 25 mg/kg per os twice weekly had significantly lower tumor weights than vehicle-treated controls, and the inhibition of tumor growth was equivalent to traditional IP paclitaxel injections. Mice that were administered DHP107 25 mg/kg twice weekly DHP107 50 mg/kg once a week showed a reduction in tumor weight, but the difference was not statistically significant.

Oral administration of paclitaxel has several important

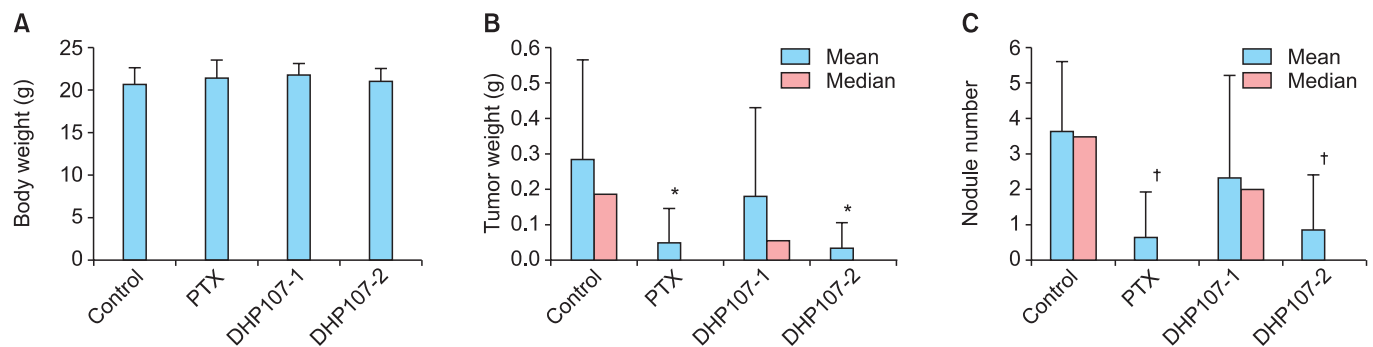


Fig. 3. To evaluate the potential therapeutic effect of DHP107 metronomic chemotherapy, mice were treated with DHP107 per os at 0 or 50 mg/kg once a week or 25 mg/kg twice per week. DHP107-1 and DHP107-2 represent DHP107 per os at 50 mg/kg once a week and DHP107 per os at 25 mg/kg twice per week, respectively. Paclitaxel (PTX) intraperitoneal injections at 5 mg/kg were used for comparison. (A) Body weight. (B) Tumor weight (* $p < 0.01$). (C) Number of tumor nodules ($^{\dagger} p < 0.01$).

advantages over intravenous (IV) or IP injection, including minimal medical supervision, no or only short-term hospitalization, and minimal risk of infection. Therefore, patients could receive treatment at home while participating in normal daily activities and maintaining a high quality of life [18,19]. Oral paclitaxel treatment, however, is clinically limited due to its insolubility in water [20], and thus IV Taxol is formulated in a mixture of ethanol and Cremophor EL to stabilize emulsions of nonpolar paclitaxel in aqueous systems. Cremophor EL, however, causes more drug-related hypersensitivity reactions than the drug itself, characterized by dyspnea, flushing, rash, chest pain, tachycardia, hypotension, angioedema, and generalized urticaria [21]. Oral paclitaxel also has poor bioavailability due to P-gp and CYP3A4. To increase the systemic absorption of oral paclitaxel, P-gp and CYP3A4 inhibitors have been used with cyclosporine, ritonavir, and GF120918 [22-24]. Although the systemic absorption increased 8- to 10-fold with the concomitant administration of inhibitors with oral paclitaxel, there were many complications related to immunosuppression and drug interactions [24]. DHP107 is an efficient lipid-based oral paclitaxel administered without Cremophor EL that is bioavailable despite the lack of concomitant P-gp inhibitors. Therefore, DHP107 has advantages over other oral paclitaxel formulations that require P-gp and/or CYP3A4 inhibitors.

Oral chemotherapy may offer increased efficacy and fewer side effects because appropriate systemic drug concentrations can be maintained continuously [16]. Metronomic therapy, or low, non-toxic doses of chemotherapy drugs administered at more frequent intervals without long rest periods, effectively reduce tumor growth by strongly suppressing tumor angiogenesis in various tumor models [12,25].

The rationale for metronomic chemotherapy is that decreasing the time between cycles prevents recovery of the damaged tumor vasculature. Further, activated tumor-associated vascular endothelial cells may be more sensitive to lower doses of chemotherapeutic agents than normal cells or cancer cells [26]. Thus, metronomic dosing of standard chemotherapeutic agents may maximize the growth-limiting effects on the tumor vasculature, overcoming the resistance or recurrence encountered with traditional dosing schedules. Additionally, metronomic chemotherapeutic regimens deliver substantially lower cumulative doses of cytotoxic agents, thereby decreasing potential side effects and improving patient tolerance [11].

In the present study, mice treated with low-dose metronomic DHP107 (25 mg/kg) twice weekly showed a greater decrease in tumor weights than those treated with high-dose DHP107 (50 mg/kg) once a week. The effect of metronomic oral treatment on the inhibition of tumor growth was equiva-

lent to that of traditional IP paclitaxel injections. Our results suggest that metronomic oral chemotherapy with DHP107 is an effective alternative method to paclitaxel IP *in vivo*. A coordinated DHP107 treatment schedule increases the *in vivo* efficacy more successfully than administering the entire dose at one time. However, there are some limitations in our study. First, we evaluated only two treatment dosages, 25 and 50 mg/kg of DHP107, for comparison with an IP paclitaxel treatment group and control group. A combination of a greater range of dosages with various time intervals may help to better understand metronomic chemotherapy for ovarian cancer. Second, we administered paclitaxel only through the IP route, not through the IV route. Paclitaxel is routinely administered through the IV route in patients with ovarian cancer, thus, further research with IV paclitaxel is necessary.

In conclusion, DHP107, a novel oral paclitaxel, was administered without Cremophor EL or a concomitant P-gp inhibitor. It had a favorable safety profile and was effective as metronomic chemotherapy treatment in an orthotopic mouse model of ovarian cancer. Future studies should be performed to establish the optimal metronomic dose to suppress tumors and minimize side effects.

CONFLICT OF INTEREST

Daehwa Pharmaceutical Co. supported this study by a research grant and supplying drugs and mice. Yeong-Woo Jo is a researcher of this company.

ACKNOWLEDGMENTS

This study was supported by a grant from Daehwa Pharmaceutical Co. and Gangwon Leading Industry Office and the National Research Foundation of Korea (NRF) grant (No. 2012R1A1A4A01014504) by Korean government.

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