



# Docetaxel-polymeric nanoparticle enhances radiotherapeutic efficacy in human pancreatic cancer

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**Background:** Nanoparticle therapeutics is promising platform for cancer treatment. In our previous study, we have developed polymeric nanoparticles (PNP) in which docetaxel was incorporated to reduce the side effects and improve the therapeutic efficacy, and recently finished its phase 1 clinical study in patients with solid tumors.

**Methods:** Radiotherapeutic efficacy of the docetaxel-contained PNP (DTX-PNP) in pancreatic cancer cells was determined by both *in vitro* and *in vivo* assay such as clonogenic survival assay with cancer cell lines, western blot for apoptotic cell death and tumor growth inhibition assay using several kinds of xenograft models. The tumors derived from human pancreatic cancer AsPC-1 or BxPC-3 cells were analyzed by immunohistochemistry (IHC) to detect in apoptosis and tubulin polymerization induced by DTX-PNP. The combinational therapeutic effect of DTX-PNP and ionizing radiation (IR) was evaluated *in vivo* mice models of AsPC-1 or BxPC-3 cell line-derived xenograft models and patient-derived xenograft model, and compared to that of reference drugs.

**Results:** DTX-PNP in combination with IR showed high cytotoxicity to pancreatic cancer cells, and ultimate inhibition of cell proliferation as determined via *in vitro* assays. *In vivo* radiotherapeutic efficacy was markedly enhanced by intravenous injection of DTX-PNP comparing to Gemzar, a common chemoradiation therapeutic agent in pancreatic cancer.

**Conclusions:** These results suggested DTX-PNP can hold an invaluable and promising position in treating human pancreatic cancer as a novel and effective radiosensitizing agent.

**Keywords:** Docetaxel-polymeric nanoparticle (DTX-PNP); pancreatic cancer; pancreatic ductal adenocarcinoma (PDAC); radiotherapy; chemoradiotherapy

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## Introduction

Pancreatic cancer is a lethal cancer of which 5-year survival rate is less than 5% (1,2). Almost all of pancreatic cancer patients with the diagnosis of pancreatic ductal adenocarcinoma (PDAC) show notoriously poor prognosis and eventually almost all patients die from the disease (3,4). Several chemotherapy drugs such as gemcitabine (GEM), paclitaxel (PTX), and 5-fluorouracil are effective in the treatment of pancreatic cancer, and even several diagnosis and treatments have recently progressed, but the survival effect is still negligible (5,6). Therefore, it is urgently necessary to develop new therapeutic means for the majority of patients with pancreatic cancer.

The taxanes have been widely used in cytotoxic treatment of many solid tumors as a family of very efficient anticancer drugs (7,8). Docetaxel (DTX) has been known to be superior to PTX in clinical efficacy, but it exhibits severe side effects (9,10). Taxotere, the most famous commercial formulation of DTX contains the non-ionic surfactant Tween 80 (polysorbate 80) and 13% ethanol; the side effects caused by DTX and the solvent have significantly limited its clinical use (11). We have developed DTX-polymeric nanoparticle (DTX-PNP) in which DTX was incorporated to reduce the side effects and improve the therapeutic efficacy, and recently finished its phase 1 clinical study. In our previous report, the result of the phase 1 clinical trial of DTX-PNP including side-effect profile, pharmacokinetics, and document any observed antitumor activity was introduced (9,12).

Radiation therapy has been considered as an important treatment for various cancer treatments. Radiotherapy plays a role especially in local progress pancreatic cancer when patients have no distant disease after chemotherapy of several months (13,14). However, not all cancers respond well to radiation therapy. Increasing the radiation dose cannot be an alternative to dose enhancement because it severely damages normal tissue around the tumor, increases the possibility of wound complications and changes the cells to radiation resistance (15,16). In order to maximize the efficacy of radiotherapy, it should be aimed to simultaneously increase the killing effect on tumor tissues and reduce side effects on normal tissues. In this study, the property of DTX-PNP that was formulated to improve chemoradiotherapeutic efficacy and reduce side effects was investigated for the enhancement of radiotherapy response in pancreatic cancer for further clinical application.

## Methods

### *Clonogenic survival assay*

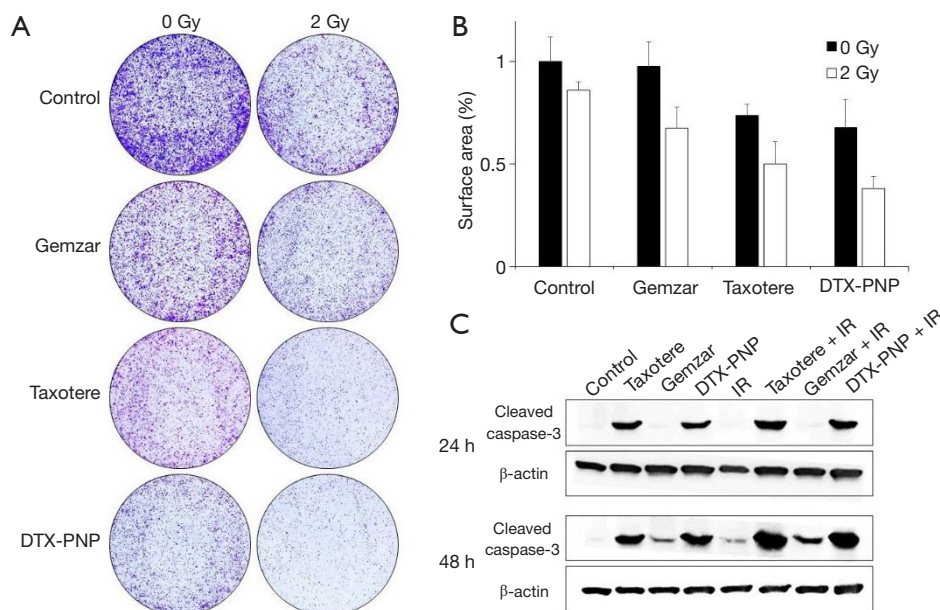
To evaluate the drug efficacy in cell proliferation and survival, cells were plated in a 6-well tissue culture plate at a density of  $5 \times 10^4$  cells/well. Cells were exposed to 2 Gy of ionizing radiation (IR) in the presence of drugs such as Taxotere, Gemzar, DTX-PNP (1 nM, 5 nM, 1 nM, respectively), and incubated for 24 h in the presence of drugs. After withdrawal of drugs from medium, cells were incubated for approximately 10 days to form colonies. Cells were stained with 0.5% crystal violet (Sigma-Aldrich, St Louis, MO), and the colony forming rate was calculated using Image J software.

### *Western blot analysis*

BxPC-3 cells treated with drugs for 24 or 48 h were harvested, washed twice with PBS, and lysed with cell lysis reagent [no. R4100-010; RIPA cell lysis buffer (1×) with EDTA, GenDEPOT] on ice. Primary antibody against cleaved caspase-3 (no. 9661; Cell Signaling Technology, Inc.) was used at 1:1,000 dilution, and HRP-conjugated secondary antibody was used at 1:2,000 dilution in 5% skim milk. After final washing, the membrane was exposed to an enhanced ECL solution and chemiluminescence image was acquired using ImageQuant LAS 4000 (GE Healthcare Life Sciences).

### *Immunohistochemical analysis*

Tumor tissue isolated from mouse was fixed in 4% paraformaldehyde overnight, permeabilized with 70% ethanol overnight. Paraffin-embedded tumor tissue was sectioned in 3  $\mu$ m, mounted on silane-coated slides. The tissue was blocked with 5% bovine serum albumin (NGS) in PBST (0.01% Triton X-100 in PBS) and incubated with anti-cleaved caspase-3 (1:1,000; no. 9661; Cell Signaling Technology, Inc.) and anti-alpha-tubulin (1:200; no. 2125; Cell Signaling Technology, Inc.) diluted in PBST overnight at 4 °C, the tissue for cleaved caspase-3 was incubated with anti-rabbit IgG-HRP (1:2,000; Jackson ImmunoResearch Laboratories, Inc.) for 1 h at room temperature and visualized with DAB (vector SK 4100). The tissue for alpha-tubulin was incubated with Alexa Fluor® 488 donkey anti-rabbit (1:500; Jackson ImmunoResearch Laboratories, Inc.) for 2 h at room temperature and visualized with VECTASHIELD



**Figure 1** *In vitro* radiosensitization effect of DTX-PNP in human pancreatic cancer cells (BxPC-3 cells). (A) Clonogenic assay of BxPC-3 cells were treated with 2 Gy of radiation and Gemzar/Taxotere/DTX-PNP; (B) the histogram shows are total area of colonies quantified; (C) western blot analysis indicates apoptosis detect of BxPC-3 at 24 and 48 h. DTX-PNP, docetaxel-polymeric nanoparticle; IR, ionizing radiation.

Mounting Media containing DAPI (Vector Laboratories).

### Tumor growth inhibition and survival fraction

All animal experiments were performed following the protocol approved by the Institutional Animal Care and Use Committee of the Asan Institute for Life Sciences. AsPC-1 or BxPC-3 cells-derived xenograft tumor model and patient-derived xenograft (PDX) tumor model made of male athymic nude mice (BALB/c nu/nu; 6 weeks old; Japan SLC, Hamamatsu, Japan) was used for the examination of *in vivo* therapeutic efficacy. To produce the xenograft model, suspension of  $1 \times 10^6$  cells and  $3 \text{ mm}^3$  tissues was implanted subcutaneously (s.c) into a right hind leg of mice. Tumors were measured by length, width and tumor volume was calculated as  $(\text{length} \times \text{width}^2) \times 0.5$ . Mice were started to receive treatment when the average tumor volume reached 80 to  $120 \text{ mm}^3$ . Taxotere and DTX-PNP at 10 mg/kg and Gemzar at 50 mg/kg were intravenously (i.v.) administrated through tail vein at 24 h after 5 Gy IR that was locally delivered to tumor using a 6-MV photon beam linear accelerator (CL/1800, Varian Medical System, Palo Alto, CA, USA).

## Results

### Radiosensitization effect of DTX-PNP in pancreatic cells

To examine radiosensitization effect of DTX-PNP, clonogenic assay survival was done with human pancreatic cancer BxPC-3 cells exposed to Taxotere, Gemzar and DTX-PNP combined with 2 Gy IR. The number of clones were much decreased by DTX-PNP and IR treatment (Figure 1). Quantificated result showed that the most effective radiosensitization was displayed by treatment of DTX-PNP and IR (Figure 1B). Combination group of IR and DTX-PNP, as well as IR and Taxotere, markedly increased cleaved caspase-3 as compared to control and IR alone (Figure 1C), suggesting that combination therapy of IR and DTX induced apoptosis higher than IR and Gemzar treatment groups. These results indicated that DTX-PNP displayed strong radiosensitization effect in human pancreatic cancer cells.

### Induction of apoptosis and tubulin polymerization in xenograft tumor tissue

To assess whether combination treatment of DTX-PNP

and IR induce apoptosis and tubulin polymerization *in vivo*, human pancreatic cancer cell-derived xenograft tumor mouse was treated and the tumor tissue was stained for cleaved caspase-3 and  $\alpha$ -tubulin. DTX-PNP and IR induced significantly potentiated apoptosis (*Figure 2A*), suggesting that DTX-PNP exhibited great radiosensitization effect *in vivo*. The ability of taxanes to bind and polymerize tubulin has been known to display anti-cancer effect. The higher the level of tubulin polymerization, the better the anti-cancer effect. In the result of tubulin staining, DTX-PNP and IR displayed effective polymerization of tubulin as likely or more than Taxotere and IR (*Figure 2B*), indicating that DTX-PNP preserved the potential of DTX and exerted the action mechanism to the *in vivo* tumor tissue. These results strongly suggested that DTX-PNP could be an effective radiosensitizer *in vivo*.

#### ***Enhanced radiotherapeutic efficacy and improved survival by DTX-PNP in various xenograft models***

To evaluate the effectiveness of DTX-PNP to enhance *in vivo* radiotherapeutic efficacy, the inhibition of tumor growth was examined in mice bearing AsPC-1 or BxPC-3 derived tumors. In both xenograft tumor models, DTX-PNP and IR treated group showed remarkably enhanced tumor growth inhibition compared to IR group, which was greater than that of Taxotere and IR or Gemzar and IR (*Figure 3A*). Mice treated with Gemzar that was the representative drug for pancreatic cancer didn't show any anti-cancer effect in these models, while Taxotere exhibited notable anti-cancer effect. Nano-particulated DTX-PNP containing DTX as active pharmaceutical ingredient was shown greater anti-cancer effect than that of free DTX, which might be due to long circulating and passive targeting. In the same context, DTX-PNP displayed the most effectively enhanced radiotherapeutic efficacy beyond Taxotere or Gemzar. Survival fraction for control, Gemzar, Taxotere or DTX-PNP treated groups of AsPC-1 were 61, 57, 71 and 75 days, respectively (*Figure 3B*). For BxPC-3, control, Gemzar, Taxotere and DTX-PNP treated groups were 35, 24, 39 and 65 days, respectively. By the combination of IR, the survivals of control, Gemzar, Taxotere were prolonged to 64, 81, 75 days in AsPC-1, and 46, 39, 85 days in BxPC-3. Importantly, the DTX-PNP combination with IR provided a substantial survival benefit that was prolonged to more than 100 days in AsPC-1, or more than 120 days in BxPC-3. There was no observable body weight loss in the mice during whole experimental

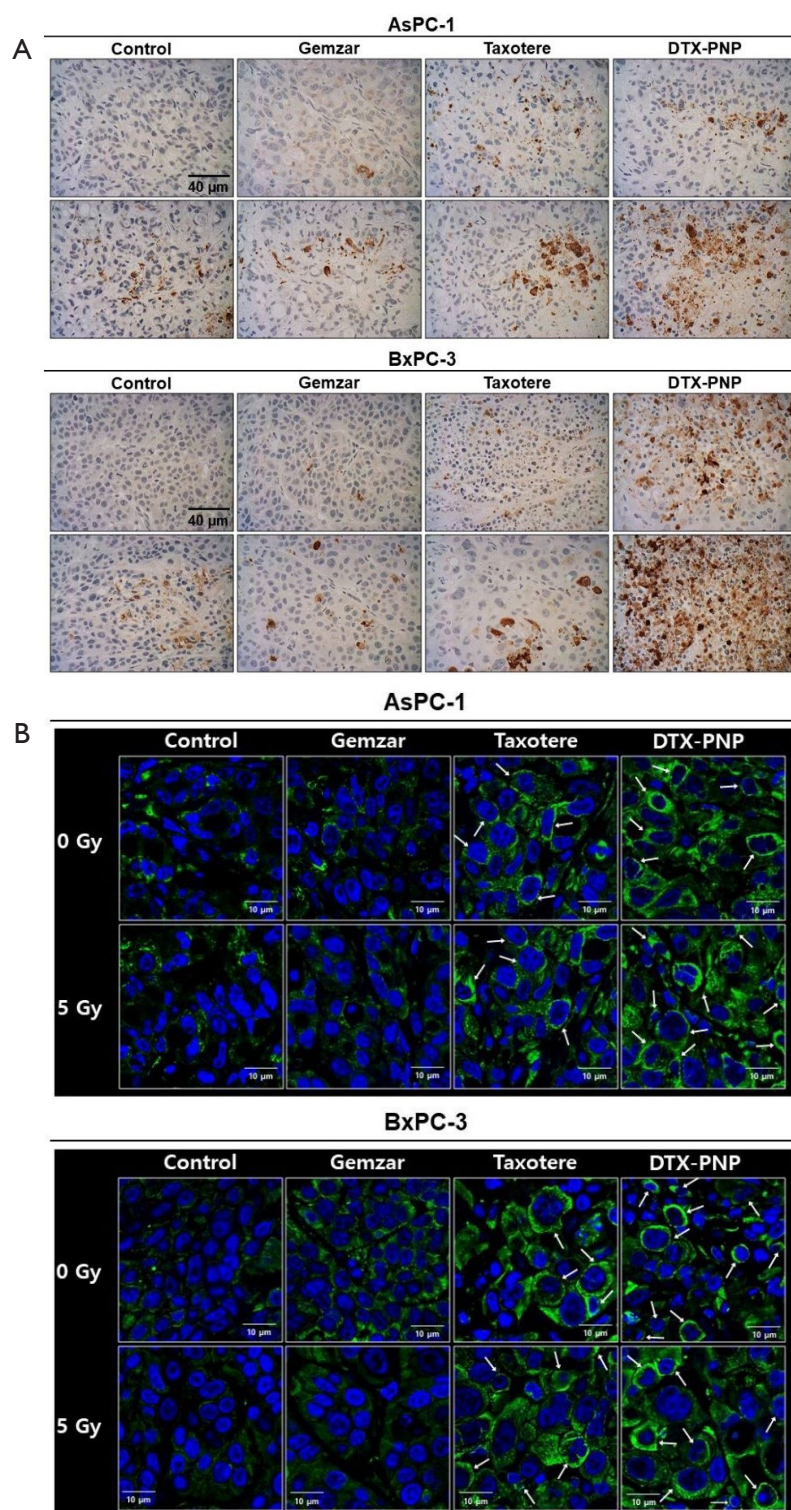
period (*Figure 3C*). These results strongly suggested that DTX-PNP greatly enhanced radiotherapeutic efficacy in animal models derived with human pancreatic cancer cells. For further evaluation of effectiveness of DTX-PNP on radiotherapy for pancreatic cancer treatment, a case of pancreatic cancer PDX model was examined. In result, DTX-PNP-treated group showed the most potent radiosensitization effect which was greater than Taxotere and similar to Gemzar (*Figure 4A*). Survival fraction for control, Taxotere, Gemzar and DTX-PNP treated group of PDX were 28, 38, 42 and 45 days, respectively. When combined with IR, the survival fraction of DTX-PNP significantly prolonged (*Figure 4B*). A change of body weight was not observed in any group, indicating that the treatments did not induce a severe toxicity (*Figure 4C*).

#### **Discussion**

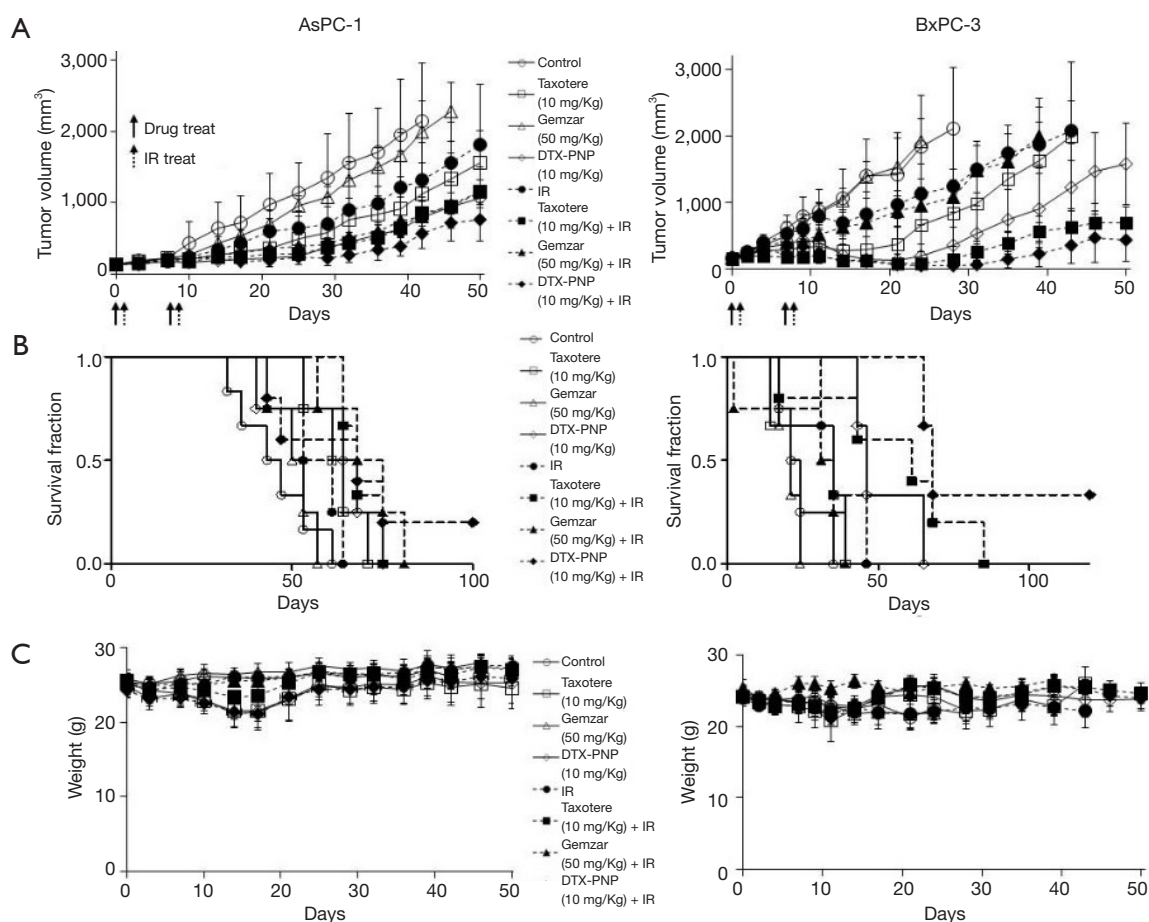
For the treatment of advanced pancreatic cancer, GEM is one of standard care (17), but large portion of patients often respond poorly to this agent. As an alternative, radiotherapy is routinely applied to patients whose tumor is neither responding to GEM nor able to be subjected to surgical intervention. Pancreatic cancer commonly encompasses major vessels named superior mesenteric artery of which circumferential contact with tumor is often a contraindication to surgery. Radiotherapy could be a solution to provide a good benefit through shrinking the circumferential contact of the vessels to allow surgical intervention, in addition to its therapeutic effect on cancer cells through induction of DNA damage leading to cell death. However, not all tumors respond well to radiotherapy, and sometimes radiotherapy could induce damages unexpectedly in healthy adjacent tissues. To overcome the current limitations in pancreatic cancer, we have tried in this study to apply DTX-PNP for the improvement of chemoradiotherapeutic efficacy and reduce adverse side effect.

This study demonstrated that DTX-PNP showed a clinically applicable effectiveness as a radiosensitizer for human pancreatic cancer. While DTX has not been approved for pancreatic cancer yet, it was proved in this study that nanoparticulated DTX showed a great efficacy in animal models of pancreatic cancer, especially in combination with radiotherapy. DTX is a well-established chemotherapeutic agent already widely used in various types of cancer, but has an obvious limit caused by toxicity in expanding the scope of application. In order to overcome the limitation of toxicity and simultaneously to maximize





**Figure 2** Tissue apoptosis and tubulin polymerization in pancreatic cancer tissue. (A) Representative image of immunohistochemical staining to detect apoptosis. Apoptotic cells were stained as brown cells and nuclear stained blue (DAB) (scale bar, 40  $\mu$ m); (B) immunofluorescence analysis for  $\alpha$ -tubulin (green) and nuclear staining (DAPI, blue). Arrows indicate tubulin polymerization (scale bar, 10  $\mu$ m). DTX-PNP, docetaxel-polymeric nanoparticle.

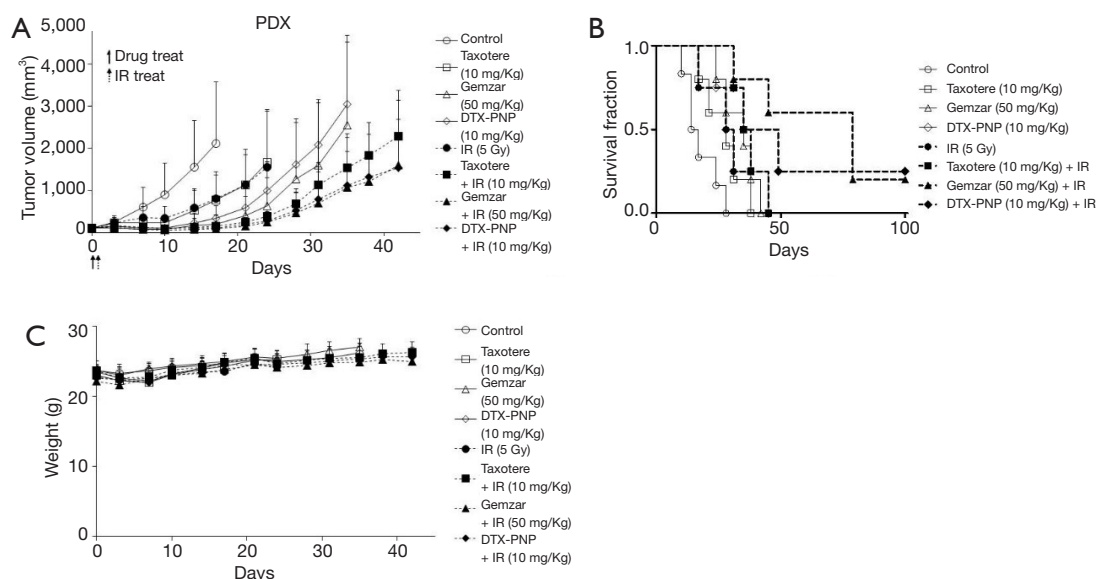


**Figure 3** *In vivo* radiosensitization effect of DTX-PNP in pancreatic cancer subcutaneous xenograft model. (A) AsPC-1 and BxPC-3 tumor growth in mice treated with control (saline), Gemzar, Taxotere (docetaxel), DTX-PNP, radiation (IR), Gemzar with radiation (Gemzar + IR), Taxotere with radiation (Taxotere + IR) and DTX-PNP with radiation (DTX-PNP + IR); (B) overall survival of xenograft mice was analyzed by Kaplan-Meier method. The survival time meant number of days in which tumor volume reaching to 1,500 mm<sup>3</sup>; (C) average body weight change during the experiment. The observed reduction in Taxotere and DTX-PNP but, restored again. DTX-PNP, docetaxel-polymeric nanoparticle; IR, ionizing radiation.

therapeutic effect, we have manufactured DTX-PNP (11). The excellent anti-cancer effect of DTX-PNP was confirmed through non-clinical studies (9), and the safety of human was verified by phase I clinical study (12). In this study, we examined the effects of DTX-PNP as a concurrent treatment with radiotherapy on pancreatic cancer, the most difficult cancer to treat. The results of this study clearly indicate that DTX-PNP can be applied to the treatment of pancreatic cancer and that rapid development and clinical feasibility will be possible because of the advantages of nanomedicine.

Number of nanomedicine has been recently developed

in various cancer types, including pancreas cancer (8). Nanoalbumin bound PTX (Abraxane) has been approved in metastatic pancreatic cancer in combination with Gemzar (6). Liposome-incorporated irinotecan (Onivyde) has been approved and shown an effect in pancreatic cancer in combination with 5-fluorouracil (5-FU) (18). Although nanoparticles have begun to be applied to pancreatic cancer, no nanomedicinal drug has yet been developed as a combination therapy for radiation therapy. This study suggests that DTX-PNP is a highly promising drug for radiation therapy to treat human pancreatic cancer and expected to be the fastest clinical application.



**Figure 4** Radiosensitization effect of DTX-PNP in pancreatic cancer patient-derived xenograft (PDX) model. (A) Tumor growth inhibition in PDX models treated with control (saline), Taxotere (docetaxel), Gemzar, DTX-PNP, radiation (IR), Taxotere with radiation (Taxotere + IR), Gemzar with radiation (Gemzar + IR) and DTX-PNP with radiation (DTX-PNP + IR); (B) overall survival of PDX mice was analyzed by Kaplan-Meier method; (C) change of body weight of PDX mice. DTX-PNP, docetaxel-polymeric nanoparticle; IR, ionizing radiation.

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## Footnote

**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2018.01.09>). The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study

was approved by the Institutional Animal Care and Use Committee of the Asan Institute for Life Sciences (No. 2017-12-026) in compliance with the national and institutional guidelines for the care and use of animals.

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