News Release

Title

Evaluation of usefulness of folate-modified cyclodextrin for new ovarian cancer chemotherapy

Key Points

- The folate-appended cyclodextrin drug carrier is potentially useful for treatment of ovarian cancer peritoneal dissemination.
- Paclitaxel dissolved with the folate-appended cyclodextrin drug carrier did not decrease neutrophil ratio in mice.
- The folate-appended cyclodextrin drug carrier targets PCFT-positive ovarian cancer cells in FRa-independent manner.

Summary

The properties of a folate-appended β-cyclodextrin-based drug carrier bound with paclitaxel (PTX/Fol-c_1-β-CyD) in xenograft mouse model of ovarian cancer peritoneal dissemination is evaluated by the team led by Specially Appointed Professor Akihiro Nawa and Visiting Researcher Shinichi Saito (R&D Department, Medical Corporation Kishokai) at Nagoya University Graduate School of Medicine Graduate School of Medicine, Obstetrics and Gynecology Industry-Academia Collaborative Research Laboratory, and collaborators including Professor Fumitaka Kikkawa and Associate Professor Hiroaki Kajiyama at Nagoya University Graduate School of Medicine, Department of Obstetrics and Gynecology. They demonstrated that PTX/Fol-c_1-β-CyD has higher antitumor effect than paclitaxel alone. In addition, no decrease in neutrophil ratio was observed in mice treated with PTX/Fol-c_1-β-CyD, suggesting suppression of side effects by paclitaxel. Furthermore, they found that proton-coupled folate transporter (PCFT) is targeted by Fol-c_1-β-CyD in addition to FRα, the previously known target. The results of this study will be useful in developing specific chemotherapy using molecular targeted drugs for ovarian cancer treatment and for other clinical application of FRα-targeted therapy.

The results of this research were published online in the Japanese Cancer Association official magazine, Cancer Science on March 10, 2020.

Research Background

Paclitaxel, which is the first-line chemotherapeutic agent used for treatment of ovarian cancer, is difficult to dissolve in water, so is dissolved using a solvent, but the solvent causes side effects such as neutropenia, which may reduce the therapeutic effect of chemotherapy. Cyclodextrin, a cyclic oligosaccharide, has been proven to be safe for human due to its track

record of use as a pharmaceutical additive. In recent years, due to the property of cyclodextrin that the outer periphery is hydrophilic and the internal cavity is hydrophobic, cyclodextrin is expected to be used as a safe solvent for anticancer drugs such as paclitaxel. Folate receptor α (FRα) that binds folate with high affinity is overexpressed in epithelial ovarian cancers. That is why folate is attracting attention as molecular targeted drug for treatment of epithelial ovarian cancer. The research group evaluated the efficacy of folate-appended β-cyclodextrin (Fol-c_1-β-CyD; Figure 1), a newly developped compound in which folates are bound to the periphery of β-cyclodextrin.

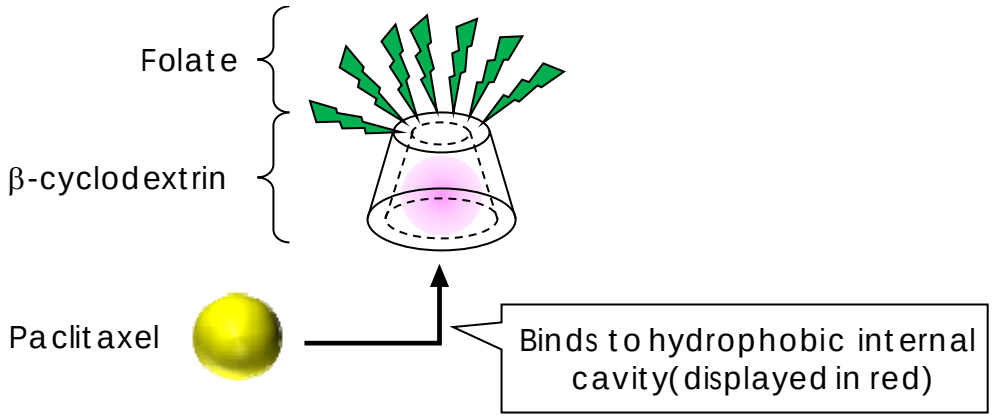

Figure 1. Binding mode of Folate-appended β-cyclodextrin and paclitaxel

Research Results

Paclitaxel (PTX/Fol-c_1-β-CyD) dissoleved with Fol-c_1-β-CyD killed the conventional target of FRα-expressing ovarian cancer cell lines, while it was also found that ovarian cancer cell lines negative for FRα expression and positive for proton-coupled folate transporter (PCFT) were also damaged. Each FRα-positive (Figure 2A) or FRα-negative/PCFT-positive (Figure 2B) ovarian cancer cell line was engrafted intraperitoneally, and then, saline, paclitaxel (5 mg/kg) or PTX/Fol-c_1-β-CyD (the paclitaxel content was equal to that of the paclitaxel-administered group) was administered intraperitoneally. PTX/Fol-c_1-β-CyD showed strongest antitumor effect. Neutrophil ratio to total blood cell count in PTX/Fol-c_1-β-CyD-administered mice showed no significant difference between saline-administered mice, suggesting that the use of PTX/Fol-c_1-β-CyD as a solvent can suppress side effects by paclitaxel.

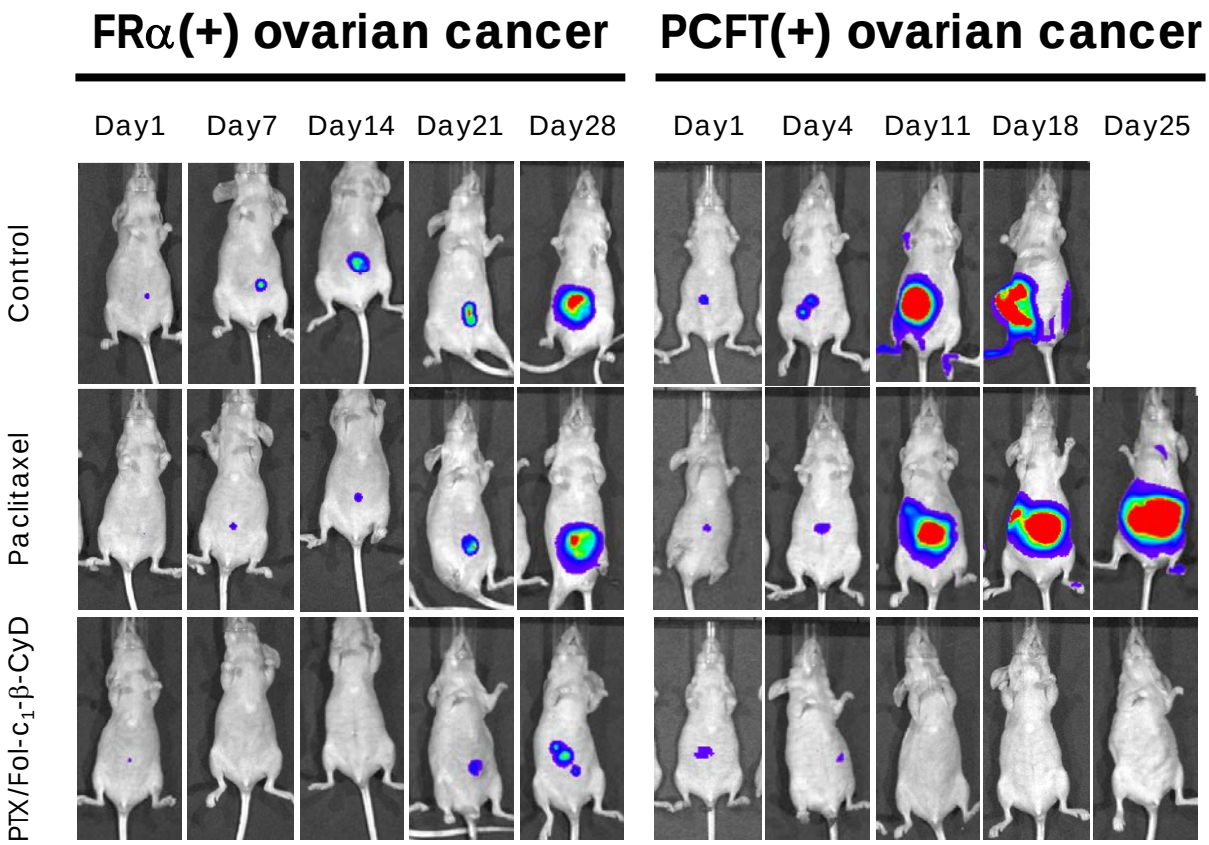

Figure 2. Antitumor effect in xenograft mouse model of peritoneal dissemination of ovarian cancer

Research Summary and Future Perspective

This study suggested that Fol-c_1-β-CyD may be a promising drug carrier in chemotherapy for ovarian cancer peritoneal dissemination. So far, there was a problem that the dose of anticancer drugs was limited by the appearance of side effects, which reduced the therapeutic effect, but it is expected that the use of Fol-c_1-β-CyD may improve this effect.

The relationship between PCFT and cancer has recently been rapidly studied. In normal tissues, PCFT expression is localized to the intestinal endothelium, but in cancer tissues, solid tumors such as ovarian cancer, liver cancer, pancreatic cancer, malignant pleural mesothelioma, and non-small cell lung cancer. Fol-c_1-β-CyD may be applicable not only to ovarian cancer but also to those solid cancers.

Publication

Shinichi Saito[1,2], Yoshihiro Koya[1,2], Hiroaki Kajiyama[3], Mamoru Yamashita[2], Fumitaka Kikkawa[3], Akihiro Nawa*[1,2]

[1]Bell Research Center, Department of Obstetrics and Gynecology Collaborative Research, Nagoya University Graduate School of Medicine, Aichi 466-8550, Japan

[2]Bell Research Center for Reproductive Health and Cancer, Medical Corporation Kishokai, Aichi 460-0003, Japan
[3]Department of Obstetrics and Gynecology, Nagoya University Graduate School of Medicine, Aichi 466-8550, Japan
*Corresponding author
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