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Polymeric micelles loaded with (1,2-diaminocyclohexane)platinum(II) against colorectal cancer

Takako Nirei, MD, Soichiro Ishihara, MD, PhD, Toshiaki Tanaka, MD, PhD, Tomomichi Kiyomatsu, MD, PhD, Kazushige Kawai, MD, PhD, Keisuke Hata, MD, PhD, Hioaki Nozawa, MD, PhD, and Toshiaki Watanabe, MD, PhD*

Faculty of Medical Sciences, Department of Surgical Oncology, The University of Tokyo, Tokyo, Japan

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ABSTRACT

Background: We investigated the potential of nanomedicine in loading the oxaliplatin parent complex (1,2-diaminocyclohexane)platinum(II)-loaded polymeric micelles (DACHPt/m) against multiple liver metastases from colon cancer in a mouse model.

Materials and methods: The efficacy of DACHPt/m or oxaliplatin (on days 14 and 21 after inoculation of tumor cells) was evaluated in a mouse model of liver metastasis for murine colon adenocarcinoma C26 cells. *In vivo* antitumor effects were evaluated by recording the number of liver metastases and weights of metastatic livers after treatment (day 28). The accumulation of drugs in tumors and liver parenchyma was analyzed using ion coupled plasma-mass spectrometry 24 h after administration of DACHPt/m or oxaliplatin ($n = 5$). We assessed renal and hepatic toxicities through changes in creatinine, aspartate transaminase, and alanine transaminase on the last day of the antitumor activity experiment.

Results: Mice receiving DACHPt/m had significantly fewer metastatic nodules ($P = 0.038$) and lower liver weights ($P = 0.038$) than those receiving oxaliplatin. The accumulation of DACHPt/m in the metastatic liver was significantly higher than that of oxaliplatin, whereas the distribution of micelles in healthy liver tissues was limited. Mice treated with DACHPt/m also showed significantly lower serum creatinine levels than those treated with oxaliplatin ($P = 0.007$), whereas serum aspartate transaminase and alanine transaminase levels for both drugs were not different.

Conclusions: High levels of DACHPt/m accumulate in metastatic livers, producing a strong antitumor effect without severe adverse effects. DACHPt/m is a safe approach for managing liver metastasis from colorectal cancer.

* *Corresponding author*. Department of Surgical Oncology, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, Japan. Tel.: +81 3 3815 5411x33246; fax: +81 3 3811 6822.
E-mail address: soichiro.ishihara@gmail.com (S. Ishihara).

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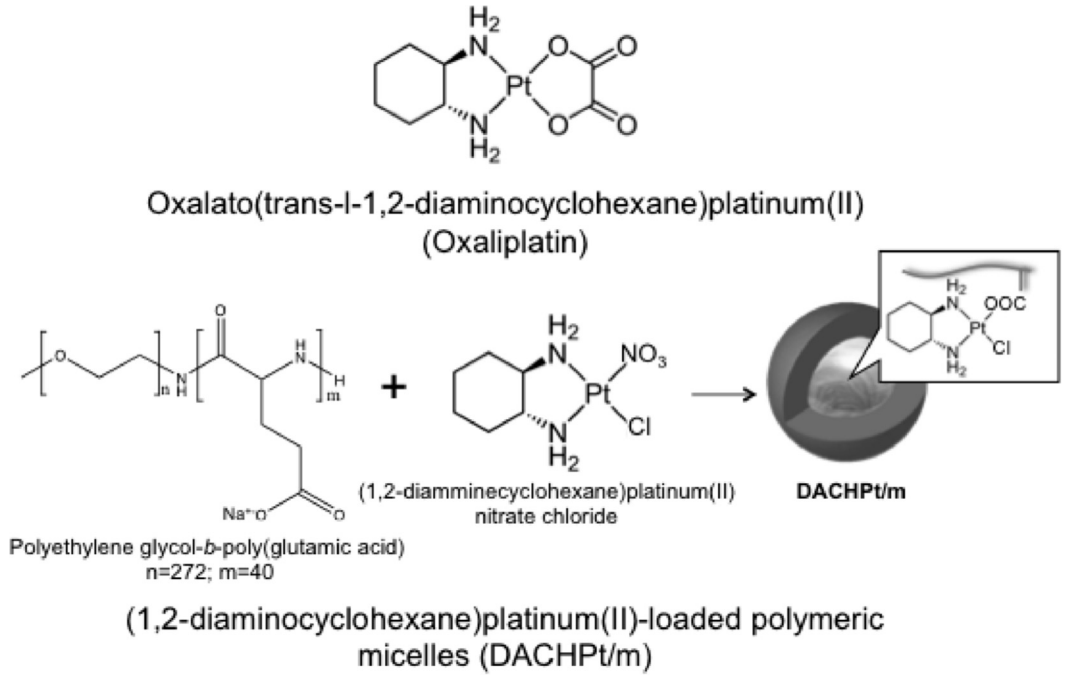

Fig. 1 – Chemical structure of oxaliplatin and scheme of (1,2-diaminocyclohexane)platinum(II)-loaded micelles (DACHPt/m).

Introduction

Colorectal cancer is a major cause of global morbidity and mortality.[1,2] Although the standard treatment for colorectal cancer is surgical removal, approximately 80% of these patients develop liver metastases.[3] Oxaliplatin [(*trans*-1,2-cyclohexanediamine)oxalatoplatinum(II); Fig. 1], a third generation platinum-based drug, is a first-line agent for treating advanced colorectal cancer. It is frequently combined with 5-fluorouracil/folinic acid, so called FOLFOX.[4,5] Despite major improvements in the survival of colorectal cancer patients, oxaliplatin-based treatments are significantly limited by severe side effects and the eventual development of drug resistance and tumor relapse. Thus, therapeutic strategies capable of safe and effective suppression of liver metastasis are still strongly desired.

Nanomedicine has the ability to develop effective treatments with reduced adverse effects.[6] Compared with conventional chemotherapy where drugs systemically diffuse, resulting in indiscriminate exposure to both tumor and normal tissues, the nanoscaled dimensions of nanomedicines allow them to selectively distribute to solid tumors based on the enhanced permeability and retention effect, which is driven by the leaky vasculature of tumor tissues and their poor lymphatic drainage.[7,8] Among clinical translational nanomedicine, drug-loaded polymeric micelles display unique ability to enhance the delivery of anticancer agents to solid tumors by stabilizing drug circulation in blood, high tumor accumulation, and controlled drug release. Several clinical trials of micelle formulations are ongoing.[9]

Polymeric micelles that deliver the oxaliplatin parent complex (1,2-diaminocyclohexane)platinum(II) (DACHPt) has higher efficacy than oxaliplatin against several tumor models,[9-14] including oxaliplatin-resistant colon adenocarcinoma tumors.[15] In addition, polymeric micelles reduce the side effects associated with oxaliplatin treatment, such as neurotoxicity.[16] These promising features of DACHPt-loaded micelles (DACHPt/m; Fig. 1) promoted their translation into phase I clinical studies.[9] We evaluated the antitumor effects of DACHPt/m against a model of liver metastasis of colorectal cancer to explore their potential as a therapeutic strategy for managing advanced colorectal cancer.

Materials and methods

Reagents, cell lines, and mice

Oxaliplatin was purchased from the Tokyo Chemical Industry Co (Tokyo, Japan). We synthesized DACHPt/m as previously described.[12] The diameter of DACHPt/m was 30 nm, as determined by Zetasizer (Malvern, UK). The Pt content in the micelles was determined by ion-coupled plasma-mass spectrometry (Hewlett Packard 4500, Agilent Technologies Inc, Santa Clara, California). A murine colon adenocarcinoma C26 cell line was purchased from the American Type Culture Collection (Denver, Colorado) and cultured in Roswell Park Memorial Institute 1640 medium (Sigma–Aldrich, St. Louis, Missouri), supplemented with 10% fetal calf serum, 50 U/mL penicillin/streptomycin (Gibco BRL, Grand Island, New York), and incubated in 5% CO_2 humidity air condition at 37°C. Six-week-old female BALB/c mice were purchased from Charles River Japan (Yokohama, Japan) and maintained under specific pathogen-free conditions throughout the experiment. All