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Factors contributing to carboplatin blockade and interruption in its route of administration in paclitaxel-carboplatin therapy

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SUMMARY The interruption of anticancer infusion processes in patients undergoing chemotherapy may affect their quality of life and the efficacy and safety of the therapy. We experienced several interruptions of carboplatin infusion in multiple patients receiving paclitaxel-carboplatin combination therapy. Therefore, we investigated the causes of these interruptions. The filter and catheter surfaces were evaluated by scanning electron microscopy. Moreover, using a texture analyzer, the mechanical strengths of catheter-attached syringes were compared pre- and post-administration. We observed that the syringe pushing force requirement was higher following dripping failure. However, precipitates were not evident on the filter surfaces, regardless of the dripping failure route. In this case, some of the drug adhered to the catheters' surfaces and interrupted the carboplatin titration. Consequently, in patients receiving combination therapy with paclitaxel and carboplatin, and experiencing interruptions in carboplatin infusion, attention should be paid to the catheter.

Keywords adsorption, catheters, scanning electron microscopy, syringe pushing force

The incidence of cancer is increasing with the aging population and mirrored by the rising number of patients undergoing cancer chemotherapy. Recently, several cancer chemotherapies have become available on an outpatient basis, allowing recipients access to treatment daily. Multiple medical devices are employed for administering anticancer drugs, including intravenous catheters, in-line filters, and closed-system drug transfer devices (*1*). In clinical practice, antiemetic agents, including serotonin (5HT3) receptor antagonists, dexamethasone, and fosaprepitant are used for preventing chemotherapy-induced nausea and vomiting. In addition, histamine H1 and H2 receptor antagonists act as prophylactic measures against allergies to anticancer drugs, such as paclitaxel, which are administered intravenously before initiating chemotherapy. Therefore, it is essential to appropriately assess anticancer drug compatibility with other drugs administered *via* the same route. Additionally, medical devices made of non-polyvinyl chloride materials should be utilized to avoid exposure to diethylhexyl phthalate during the administration of intravenous anticancer drugs, such as etoposide (*2*). Data on the interactions between anticancer drugs and medical devices during intravenous administration are currently limited.

We encountered several patients with ovarian cancer who were treated with paclitaxel and carboplatin (TC) therapy (*3*) and who could not receive the full dose of carboplatin owing to failure of carboplatin titration post paclitaxel administration. All patients had plastic peripheral intravenous catheters placed in their arms and had received fosaprepitant, meglumine, palonosetron, dexamethasone, chlorpheniramine, and famotidine from the same peripheral route before paclitaxel administration. If carboplatin could not be titrated, the infusion was improved slightly by administering saline before restarting carboplatin. However, despite frequent notifications by the infusion monitor alarm, saline and carboplatin were often administered alternately. The eventual outcome in these cases would be the complete removal of the peripheral intravenous catheter and replacement of all peripheral routes, which is a heavy burden on patients and nurses. While anticancer drugs are routinely administered *via* a plastic indwelling peripheral intravenous catheter placed in a vein in the arm or another body part, there is little information available on the interactions between the catheter material and the drugs. We identified the cause of blockage on the inner surface of these devices and compared the pushing force of blocked and unblocked catheters.

We investigated the cause of blockage using

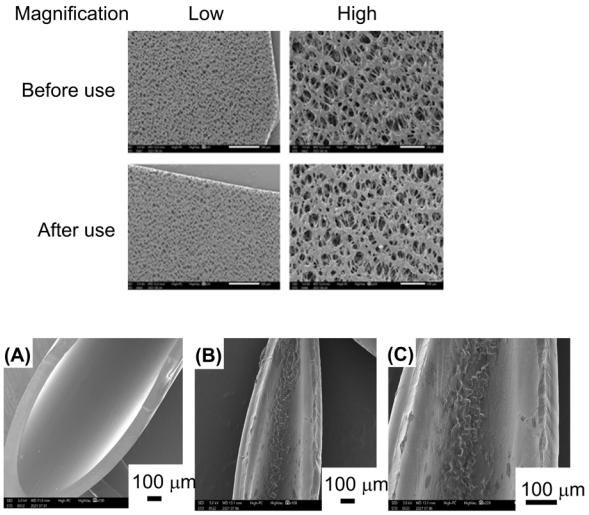

Figure 1. (Top): Visual and SEM images of the filter along the infusion route post administration of a TC regimen. (Bottom): SEM images of the catheter surface (A) saline immersion (B) low and (C) high magnification of catheter cross-section post administration of TC regimens.

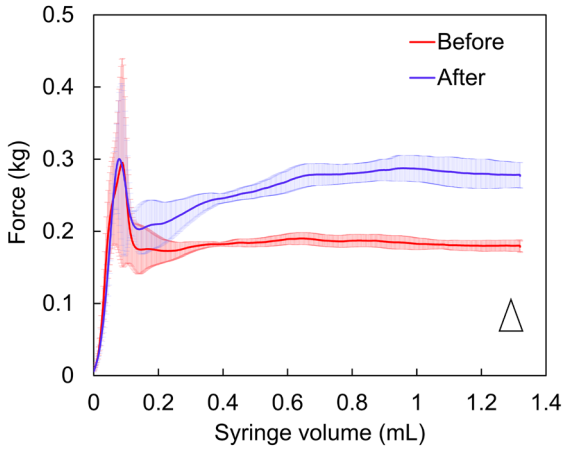

Figure 2. Comparison of catheter extrusion force before and after paclitaxel and carboplatin administration. Triangle indicates the value used for evaluation. Error bars represent standard deviations (n = 5).

an infusion set filter membrane and catheter used by a patient who could not titrate carboplatin after receiving paclitaxel with a TC regimen. The absence of precipitates in the bottle containing the solution to be infused was confirmed before detailed observation. The microstructures of the surfaces of the infusion set filter membranes and the catheter, obtained after the TC regimen, were assessed using JCM-7000 scanning electron microscopy (SEM) (JEOL Ltd. Tokyo, Japan). The disassembled in-line filter and catheters were immersed in distilled water for desalination. Post drying, they were coated with osmium tetroxide (OsO_4) and observed by SEM. Additionally, we evaluated the catheter extrusion force before and after paclitaxel and carboplatin administration. A syringe was filled with 5 mL water to prevent the entry of air, followed by placing a catheter at the tip, which was subsequently set in a TX-TA Plus texture analyzer (Stable Micro Systems, UK). The experimental conditions were compression at 2 mm/s, and measurements were stopped after the syringe had been pushed out and moved by 10 mm. The passage of a total amount of 1.32 mL water through the catheters was evaluated and force–distance plot for 5 s was recorded. Paclitaxel IV Infusion Hospira (Pfizer Japan Inc., Tokyo, Japan) and carboplatin NK injection (Mylan Inc., Tokyo, Japan) were utilized. Terufusion™ (Terumo Co. Tokyo, Japan) and Surshield SURFLO 2 (Terumo Co.) were used as the route and catheter, respectively. Post administration, the catheter was rinsed with deionized water, dried *in vacuo* at room temperature, and used for further examination. Blockade after drug administration was evaluated by assessing the extrusion force of the syringe, which was connected by a tube. Statistical significance was set at a $p < 0.05$, and data were analyzed using Microsoft Excel.

Visual and SEM images of the filter along the infusion route post administration of the TC regimen were identical in all aspects to an unused sample with no evidence of adsorption on the filter surface (Figure 1). Figure 1 (top) shows the SEM images of the catheter cross-sectional surface. As shown in Figure 1 (bottom), the surface of the control catheter, immersed in saline for 3 h was smooth, without any evidence of precipitates. By contrast, precipitates were observed on the catheter surface post paclitaxel and carboplatin administration (Figure 1, bottom, B and C). Figure 2 compares catheter extrusion force before and after paclitaxel and carboplatin administration. The extrusion force of five catheters at the end of the extrusion in the unused product (1.32 mL; open circle) was 0.179 ± 0.008 kg. The pushing force determined after five experimental procedures that involved duplicate or triplicate readings using two catheters was 0.277 ± 0.018 kg. There was a significant difference in the catheter extrusion force before and after paclitaxel and carboplatin administration ($p < 0.01$).

We investigated the cause of carboplatin infusion interruption in a patient receiving a TC regimen. The surfaces of filters and catheters were evaluated using SEM. A texture analyzer was used to compare the mechanical strength of syringes and catheters before and after administration. There was no sediment on the filter surface; however, there was sediment on the catheter surface, resulting in higher syringe push force requirements. We found that adsorption to the catheter surface causes interference and interruption of carboplatin.

Following paclitaxel and carboplatin administration, a higher force of approximately 0.5 kg was required for catheter extrusion force compared to that required by an unused one. Furthermore, since the observation

was made in the dry state, the perceived thickness may have been less than that of the actual precipitate. When patients receiving combination therapy with paclitaxel and carboplatin experience interruptions in carboplatin infusion, attention should be paid to the catheter as well as the filter.

Catheter blockages pose two significant issues. First, there is the risk of a puncture during catheter replacement. While none of our patients complained of vascular pain while flushing with saline, there are reports of its occurrence in carboplatin-containing regimens (*4*). Second, prolonged carboplatin infusion time may adversely affect its efficacy or augment associated side effects. Adverse events, including increased myelosuppression, have not yet been reported in the context of carboplatin treatment. However, increased myelosuppression has been reported with prolonged infusion of gemcitabine (*5*). Evidence-based medicine mandates that healthcare professionals strictly adhere to the recommended dosages and administration rates during anticancer treatments, which have been confirmed to be effective and safe in clinical trials. Furthermore, doctors and nurses are well-familiarized with the usage of devices, such as catheters and filters, during drug administration. However, in the context of interactions between devices and therapeutic agents, pharmacists play a central role in scientifically establishing the physical properties of the materials used in devices and drugs. Thus, appropriate awareness of interactions between devices and drugs is essential to ensure effective and safe chemotherapy. This report will aid pharmacists in avoiding dose discontinuation scenarios caused by interactions between devices and therapeutic agents.

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References

1. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. Am J Health Syst Pharm. 2006; 63: 1172-1193.
2. de Lemos ML, Hamata L, Vu T. Leaching of diethylhexyl phthalate from polyvinyl chloride materials into etoposide intravenous solutions. J Oncol Pharm Pract. 2005; 11:155-157.
3. Parmar MK Ledermann JA, Colombo N, *et al*. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: The ICON4/AGO-OVAR-2.2 trial. Lancet. 2003; 361:2099-2106.
4. Nagase S, Fukazawa T, Uehara N, Fujimori R, Watanabe T, Shimizu K, Aizawa Y, Kanno H. The effectiveness of a glucose solution for vascular pain in patients who received line flushing after administration of carboplatin based regimens. Jpn J Pharm Palliat Care Sci. 2017; 10: 35-40. (in Japanese)
5. Grunewald R, Abbruzzese JL, Tarassoff P, Plunkett W. Saturation of 2′,2′-difluorodeoxycytidine 5′-triphosphate accumulation by mononuclear cells during a phase I trial of gemcitabine. Cancer Chemother Pharmacol. 1991; 27:258-262.

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