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Case Report

Premedication with fast-acting oxycodone hydrochloride hydrate effectively reduced oxaliplatin-induced severe vascular pain

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ABSTRACT

Oxaliplatin is a platinum-based chemotherapeutic agent that holds a prominent position in the treatment of colorectal and gastric cancers. However, severe oxaliplatin-related vascular pain can be problematic for patients. Here we describe seven patients who experienced severe vascular pain caused by oxaliplatin administration. All seven patients were treated with capecitabine and oxaliplatin or capecitabine plus oxaliplatin with bevacizumab as an adjuvant or a treatment for recurrent colorectal cancer, respectively. Patients experienced intolerable vascular pain during oxaliplatin administration, which continued for several days. Moreover, vascular pain also induced insomnia and appetite loss in all patients. We recommended implantation of a central venous (CV) port to the patients; however, all patients declined this treatment. In addition, various known countermeasures were taken, but were ineffective. Therefore, patients were orally administered oxycodone hydrochloride hydrate (Oxinorm®) 45 min prior to oxaliplatin administration. This pretreatment successfully reduced vascular pain and improved subsequent chemotherapy. Oxinorm® is a fast-acting opioid that can be an effective and practical option for severe vascular pain induced by oxaliplatin. The present report is the first description that emphasizes the usefulness of Oxinorm® to overcome the vascular pain induced by administration of oxaliplatin via a peripheral vein.

1. Introduction

Oxaliplatin, a promising third-generation platinum analogue, has a demonstrated activity in treatment for colorectal cancer (CRC) comparable to that of irinotecan. Chemotherapy for CRC has advanced markedly with the introduction of folic acid, fluorouracil, and oxaliplatin/irinotecan (FOLFOX/FOLFIRI), which typically require a central venous port [1–3]. However, biweekly or triweekly chemotherapy regimens without a CV port have been recently introduced. Capecitabine and oxaliplatin therapy (XELOX) is a CV port-free option for the treatment of colorectal or gastric cancer in Japan. Unlike other platinum-containing agents, peripheral neuropathy is a well-known dose-limiting toxicity of oxaliplatin [4].

Vascular pain should not be overlooked as an intolerable complication relating to oxaliplatin administration. Surprisingly, reports on vascular pain due to chemotherapy agents, including oxaliplatin, are insufficient despite its inevitability as an adverse drug reaction [5–7]. Thus, new methods to prevent vascular pain are required. We herein report seven cases of severe vascular pain due to oxaliplatin that were successfully treated with oxycodone hydrochloride hydrate (Oxinorm®). We have also reviewed and visualized the available countermeasures for vascular pain induced by oxaliplatin.

2. Patients and methods

All seven patients with CRC received treatment with XELOX or XELOX plus bevacizumab at Sanraku Hospital (Tokyo, Japan) between 2015 and 2016. The number of patients who underwent

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XELOX or XELOX plus bevacizumab at our institution in a single year between 2015 and 2016 was 45 in total. The patient cohort comprised three men and four women, who consisted of 15.5% of all the patients that underwent XELOX or XELOX plus bevacizumab at our institution in a single year between 2015 and 2016. A mean age of the patients was 53.5 ± 6.9 years. Oxaliplatin was administered according to the prescribed regimen at our institution (XELOX plus bevacizumab; 7.5 mg/kg bevacizumab and 130 mg/m^2 oxaliplatin on day 1 plus 2000 mg/m^2 capecitabine on days 1–14, 3q, XELOX; 130 mg/m^2 oxaliplatin on day 1 plus 2000 mg/m^2 capecitabine on days 1–14, 3q) [8]. Initially, the treatment regimen did not include Oxinorm® as a premedication. Rather, we routinely warmed the affected limb using hot packs. Once patients complained of intolerable vascular pain despite using hot packs, we began administering 2.5 or 5 mg Oxinorm® as a premedication approximately 45 min prior to oxaliplatin administration as shown in Table 1. Prior to administering Oxinorm® to a patient, we explained that Oxinorm® is a fast-acting opioid and conveyed its representative complications such as drowsiness, boke, and constipation. Patients received an explanation about a few words of cautions on their way home. We obtained informed consent from all patients.

Vascular pain was estimated using the numeric rating scale (NRS; Fig. 1) [8] upon oxaliplatin administration both before and after using Oxinorm® in all patients. Self-report of NRS before and after using Oxinorm® were made by and limited to the patients who hoped to obtain subsequent pain relief from oxaliplatin-induced vascular pain. Self-report of NRS both before and after Oxinorm® was estimated at the time of maximal pain regardless of date and hour. JMP 11 (SAS Institute Inc., Japan) was used for statistical analyses. NRS before and after Oxinorm® administration was compared and analyzed using a two-tailed Wilcoxon signed-rank test. Differences with a p-value of <0.05 were considered statistically significant.

3. Results

NRS decreased from 8.0 ± 1.0 to 2.7 ± 0.96 (mean ± standard deviation) after Oxinorm® administration. Oxinorm® was remarkably effective in all patients (Table 2). Vascular pain significantly decreased after Oxinorm® administration in each patient as measured via NRS ($p = 0.0002$; $p < 0.05$). Patients who had experienced intolerable vascular pain during oxaliplatin administration were thus relieved from their pain. Moreover, they showed improvements in insomnia, appetite loss, and persistent residual vascular pain after discharge. None of these patients experienced any complication associated with Oxinorm® administration with the exception of mild drowsiness in Cases 2 and 6. Thereafter, Oxinorm® was administered as a premedication for these patients, which enabled them to receive subsequent chemotherapy without further severe pain.

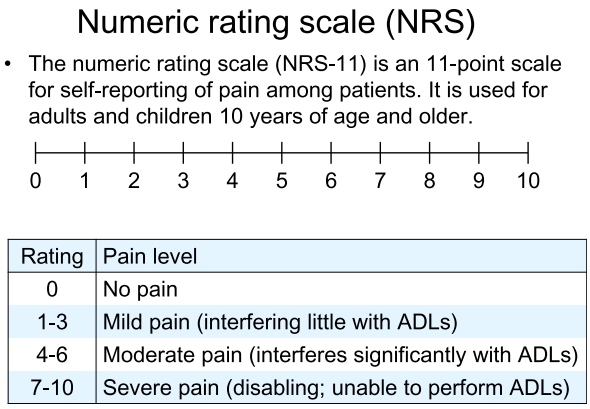

Fig. 1. The numeric rating scale (NRS-11) is an 11-point scale for self-reporting of pain among patients. It is used for adults and children 10 years of age and older. Patients expressed degrees of oxaliplatin-induced vascular pain before and after Oxinorm® administration. ADL: activities of daily living.

4. Discussion

Recently developed combined capecitabine and oxaliplatin chemotherapy (XELOX) can be administered without implantation of a CV port. This combination is an important postoperative adjuvant chemotherapy alternative as well as a therapy for unresectable or recurrent CRC worldwide. In concurrence with S-1 plus irinotecan or S-1 plus oxaliplatin, XELOX enables patients to undergo chemotherapy at outpatient chemotherapy clinics.

XELOX has several advantages as a chemotherapeutic agent. First, a CV port is not necessary for XELOX administration, as it includes only oxaliplatin as an intravenous fluid preparation. Only 3–4 h are needed to administer patients with XELOX or XELOX plus bevacizumab via a peripheral vein. Because the duration and frequency of XELOX administration are limited during standard treatment, particularly in a postoperative adjuvant setting, this feature is typically its greatest merit to patients who are required to undergo postoperative adjuvant treatment or management of

Table 1
The XELOX timetable at the chemotherapy clinic at our institution.