

CASE REPORT

Oxaliplatin-induced hypersensitivity reaction displaying marked elevation of immunoglobulin E

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A 74-year-old female has been diagnosed with stage IIIB rectal cancer in 2003. Following anterior resection, she received adjuvant chemotherapy with three different regimens. In August 2005, she was started on a modified FOLFOX6 regimen, and the sixth cycle of chemotherapy induced a severe hypersensitivity reaction (HSR). Immediate cessation of the infusion resulted in a disappearance of the allergic reaction 60 min later. Blood tests just after the reaction demonstrated a marked elevation of immunoglobulin E to 300 IU L^{-1} (normal range: $<170 \text{ IU L}^{-1}$). This change implies the involvement of a type I reaction in the HSR. In addition, a drug lymphocyte stimulating test against oxaliplatin and levofolinate calcium (an isomer of leucovorin calcium) gave values of

696% and 107 % respectively, as compared with control serum. This suggests that the patient had an adverse reaction not only of type I but partly of type IV allergic reaction also.

Oxaliplatin appears to have caused a HSR in this Japanese patient, and thus pharmacists, physicians, and other medical staff must keep a careful watch of a patient's clinical condition during chemotherapy including oxaliplatin. *J Oncol Pharm Practice* (2007) 13: 233–235.

Key words: oxaliplatin; FOLFOX; hypersensitivity reaction; anaphylaxis; immunoglobulin E

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INTRODUCTION

Oxaliplatin has been used for the treatment of metastatic colorectal cancer in combination with 5-fluorouracil (5FU) and levofolinate calcium (an isomer of leucovorin calcium) in the FOLFOX regimen, and approved worldwide. Currently, the FOLFOX and FOLFIRI (5FU, irinotecan hydrochloride

(CPT-11) and levofolinate calcium) regimens are mainly used to treat for recurrent or unresectable colorectal cancer.^{1,2}

In cancer chemotherapy, adverse drug reactions are very difficult to predict and avoid. Among adverse drug reactions, drug-induced hypersensitivity reaction (HSR) is one of the serious problems.³ Recently, an increasing number of HSRs to oxaliplatin have been reported.⁴⁻¹³ Although the incidence has been reported to be over 10% in Western populations, severe HSRs to oxaliplatin were considered rare.⁷ However, with the increase of clinical use, more than over 10% of patients experience severe allergic reactions, defined as grade 3-4.⁸

Recently, we encountered a severe and acute allergic reaction with marked elevation of immunoglobulin E (IgE) in a 74-year-old woman with rectal cancer, who received a modified FOLFOX6 (mFOLFOX6) regimen. Here, we report a HSR to oxaliplatin in this patient.

CASE REPORT

A 74-year-old female was diagnosed with stage IIIB rectal cancer in 2003. Following anterior resection she received adjuvant chemotherapy with three different regimens, 5FU and levofolinate calcium administered intravenously, doxyfluridine delivered orally or the IFL regimen (consisting of 5FU, CPT-11 and levofolinate calcium) for 2 years. She had a documented history of allergy to a contrast medium. In July 2005 she was diagnosed with metastatic disease of the liver. Chemotherapy was commenced with FOLFOX6 regimen. She received five cycles of chemotherapy (total dose of oxaliplatin 425 mg m⁻²) without significant toxicity and responded as judged by reduction of tumor markers.

During the sixth cycle, 10 min into a 2 h infusion of oxaliplatin, a severe HSR occurred, defined as grade 3 according to Common Terminology Criteria for Adverse Events v3.0, involving causing skin eruption and erythema over the entire body, facial edema, palpitations, and drop in body temperature (from 36.4°C to 35.8°C). The infusion was immediately stopped and 100 mg of hydrocortisone was administered intravenously. The symptoms resolved over the following 60 minutes.

Relevant laboratory data, measured before and just after the HSR, are shown in Table 1. Segment of white blood cell count showed a 2-fold increase, however

Table 1. Laboratory data before and after hypersensitivity reaction

		Before	After
White blood count	(μL^{-1})	4590	3150
Red blood count	($\times 10^4 \mu\text{L}^{-1}$)	362	362
Haemoglobin	(g dL ⁻¹)	11.5	11.3
Haematocrit	(%)	35.9	35.6
Platelet	($\times 10^4 \mu\text{L}^{-1}$)	18.3	17.6
C-Reactive Protein	(mg dL ⁻¹)	0.1	0.1
IgE (RIST)	(IU L ⁻¹)	–	300
<i>White blood cells</i>			
Band forms	(%)	0.0	0.0
neutrophils	(%)	32.3	62.6
Eosinophils	(%)	2.2	0.6
Basophils	(%)	0.4	0.3
Monocytes	(%)	9.8	2.5
Lymphocytes	(%)	9.8	2.5

Before and after are values at 60 min before the starting of chemotherapy and at 15 min after on set of hypersensitivity reactions, respectively.

eosinophil count was lower than before the HSR. The total IgE level was 300 IU L⁻¹.

A drug lymphocyte stimulating test (DLST) against oxaliplatin and levofolinate calcium was conducted. Values were 696% and 107% respectively as compared with control serum, indicating a positive test for oxaliplatin. Therefore, further treatment with oxaliplatin was not attempted. A FOLFIRI regimen (5FU, CPT-11 and levofolinate calcium) was adopted as the next step.

At present, this regimen was continued on her with no remarkable side effects.

DISCUSSION

Recently, an increasing number of HSRs to oxaliplatin have been reported, their reactions referred to occur either during or shortly after the infusion of oxaliplatin. In addition, several groups have reported that HSRs to oxaliplatin were experienced after a median of 7-10 cycles and cumulative dose of more than 600 mg m⁻². In the present case, the HSR occurred during the infusion of oxaliplatin and levofolinate calcium in the sixth cycle of mFOLFOX6. At the onset of HSRs, the cumulative dose of oxaliplatin was 432 mg m⁻². Immediate cessation of the infusion of oxaliplatin and the giving of hydrocortisone resulted in a recovery from the HSR. Strategies such as desensitization and prophylaxis with antihistamines and steroids were

proposed for avoiding HSRs to oxaliplatin.^{7,10} However, their effectiveness remains sufficiently unestablished. Recently, the practice of cancer chemotherapy in outpatients has been rapidly spreading in Japan. If such a HSR would occur outside of the hospital, it would presumably be life-threatening. Therefore, pharmacists, physicians, and other medical staff must understand the importance of a careful watch during and after chemotherapy, and enforce the follow-up of patients, especially in outpatients.

Several reports have demonstrated HSRs to cisplatin or carboplatin, although the mechanism of the HSRs is still unknown.^{11,12} The HSRs are considered to be mediated by IgE and/or the direct release of vasoactive substances.¹⁴ Similar mechanisms presumably participate in the case of oxaliplatin.⁶ In the present case, the IgE level displayed marked elevation at just after the onset of HSRs (normal range: $<170 \text{ IU L}^{-1}$), and this was also higher than the usual level of 120 IU L^{-1} , 2 months later from the onset. This certainly implies the participation of a type I reaction in the HSR, although the number of eosinophils was reduced.

To decide on the next approach, DLST reflecting the delayed immunological mechanism was applied. The value for oxaliplatin was extremely high (696%), being positive. This suggested that the present patient had an adverse reaction not only of type I but also of type IV, resulting in the discontinuance of oxaliplatin. Generally, DLST is considered to have variations in practice and differences or lack of lymphocyte transformation test,¹⁵ although the rapid insulin sensitivity test (RIST) method was applied to DLST in this case. Consequently, the IgE assay and DLST are considered unnecessary to do as a routine examination, but these are useful tools for selecting the next approach in the case of appearance of HSRs. Recently, the delayed HSR with severe respiratory symptoms after 24 h the infusion of oxaliplatin, was reported,¹³ and thus the mechanisms of the delayed HSR must also be clarified.

In conclusion, oxaliplatin was suggested to cause HSR *via* a type I allergic reaction displaying marked elevation of IgE level in our patient, and thus pharmacists, physicians, and other medical staff must keep a careful watch of a patient's clinical condition during chemotherapy including oxaliplatin.

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