Hypersensitivity Reactions to Oxaliplatin

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Oxaliplatin is a third-generation platinum compound that is used as a single agent and in combination with fluorouracil (5-FU) to treat colorectal and gastric carcinoma. The patients treated with oxaliplatin may develop hypersensitivity and idiosyncratic reactions, although these complications are known to be rare. We report here on two patients who suffered with metastatic colorectal cancer and who underwent palliative combination chemotherapy with oxaliplatin; they then developed hypersensitivity reactions to oxaliplatin. The first case had an anaphylactic reaction immediately after the beginning of

the 7th to 8th cycle infusion of oxaliplatin. The second case developed repeated febrile episodes from the 4th to 8th cycles of oxaliplatin infusion. With the increasing use of oxaliplatin in clinical practice, we are now encountering an increasing incidence of suspected hypersensitivity reactions. Physicians should keep their eyes wide open and carefully observe for the clinical manifestations of these hypersensitivity reactions. (*Cancer Res Treat.* 2006; 38:240-241)

Key Words: Hypersensitivity, Chemotherapy, Oxaliplatin

INTRODUCTION

Oxaliplatin is a third-generation platinum compound with a 1,2-diaminocyclohexane carrier ligand, and it is used as a single agent or in combination with fluorouracil (5-FU) to treat colorectal and gastric carcinoma. Its acute toxicities include nausea, vomiting, diarrhea, neutropenia, thrombocytopenia, peripheral sensory neuropathy and hypersensitivity reaction. Hypersensitivity reaction is a very rare adverse effect of oxaliplatin, but the incidence increases with multiple cycles of therapy (1). With the increasing use of oxaliplatin in clinical practice, we are now encountering a significant increase of hypersensitivity reactions.

To the best of our knowledge, hypersensitivity reactions associated with oxaliplatin have not yet been reported in Korea. We report here on two patients with metastatic colon cancer who developed hypersensitivity reactions to oxaliplatin.

CASE REPORT

1) Case 1

A 51-year-old woman was diagnosed with locally advanced rectal cancer (stage IIIA) on October 2001. The patient had no history of any allergic disorder. She underwent laparoscopic

lower anterior resection on January 2002 and she received concurrent chemoradiotherapy preoperatively and adjuvant chemotherapy that consisted of 5-FU and leucovorin. On September 2003, pulmonary metastases from rectal cancer developed in both lungs and she underwent complete metastectomy. After the operation, she was treated with irinotecan (150 mg/m²) every 2 weeks up to the 7th cycle. Multiple unresectable pulmonary metastases reappeared on April 2005. She was treated with oxaliplatin 85 mg/m² intravenously (IV) over 2 hours on day 1, leucovorin 200 mg/m² IV over 2 hours on days 1 and 2, and 400 mg/m² IV bolus of 5-FU followed by 600 mg/m² IV as a continuous 22 hour infusion on days 1 and 2 (FOLFOX 4). She received chemotherapy up to the 6th cycle without any side effects. She showed stable disease after the 4th cycle of chemotherapy. The patient developed severe nausea and syncope ten minutes after oxaliplatin administration at the 7th cycle. The physical examination revealed severe diaphoresis, confused mental status and the blood pressure was 90/60 mmHg. The oxaliplatin was immediately discontinued. She was treated with intravenous hydrocortisone, nasal oxygen and volume expansion. Her blood pressure and mental status improved immediately after this management. Two weeks later, with her informed permission, oxaliplatin was retried with increasing the infusion time up to 6 hours. We observed her very closely during this infusion of oxaliplatin. She received pre-medication with hydrocortisone and chlorpheniramine. She experienced nausea, sweating, severe facial flushing and dyspnea 10 minutes after oxaliplatin administration. A skin rash progressed over her entire body and the blood pressure was 140/60 mmHg. The oxaliplatin was immediately stopped and she was given hydrocortisone, chlorpheniramine, nasal oxygen and volume expansion. Within 10 minutes, her dyspnea, facial flushing and skin rash began to improve. She fully recovered 8 hours after the reaction.

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2) Case 2

A 50-year-old woman was diagnosed with colon cancer and carcinomatosis peritonei on March 2005. She was treated with FOLFOX 4 as the first-line treatment. The patient had no history of any allergic disorder. She received FOLFOX 4 up to the 3rd cycle without side effects. She experienced fever (up to 39°C) and mild chilling about 4 hours after oxaliplatin administration between the 4th and 8th cycles, and this persisted for 12 to 15 hours and then it resolved spontaneously. The tumor response was a stable disease after the 8th cycle of chemotherapy. Diclofenac was given for controlling her fever at the 9th cycle and diclofenac was given for antipyretic prophylaxis at the 10th cycle. She developed sweating and dizziness approximately 4 hours after oxaliplatin administration at the 10th cycle. The physical examination revealed hypotension (SBP <60 mmHg); she then recovered after volume infusion. We stop the FOLFOX 4 chemotherapy thereafter.

DISCUSSION

Our first patient is a case of typical anaphylactic reaction, whereas the second patient is a case of more consistent with idiosyncratic reaction.

Hypersensitivity reactions to oxaliplatin are very rare (1). The incidence of hypersensitivity reactions increases with multiple courses of the drugs and they generally occur after 4 to 6 courses (1,7). The cumulative median dose of oxaliplatin received in that previous study was 650 mg/m² (range: 100~2,400 mg/m²) (3). However, Meyer et al suggested that oxaliplatin hypersensitivity reaction has been frequently under-diagnosed, with mild symptoms being missed, and they estimated the incidence to be approximately 12% (2).

Hypersensitivity reactions related to oxaliplatin may include anaphylactic reactions and idiosyncratic reactions. The symptoms of anaphylactic reactions (type I hypersensitivity), which usually occur within minutes of administration in patients with prior exposure, include facial edema, bronchospasm, hypotension, tachycardia, pruritis and erythema. These symptoms result from the degranulation of mast cells and basophils following IgE binding to those cells. The symptoms of idiosyncratic reactions that are not antibody-related and the onset of which may be delayed include fever, chills, abdominal pain, nausea and diarrhea with or without hypotension. Idiosyncratic reactions are abnormal reactions to a drug and they are caused by the increased release of cytokines (e.g., IL-6 and TNF) from the tumor (1,4,5).

Our first case developed hypotension, dyspnea, pruritis and erythema immediately after the beginning of the 7th cycle infu-

sion of oxaliplatin. The patient's symptoms were mostly consistent with an anaphylactic reaction. In spite of premedication with steroid and antihistamine, the same symptoms recurred immediately after the retreatment. Our second case developed fever and chills about 4 hours after oxaliplatin administration. The patient's symptoms were mostly consistent with idiosyncratic reaction. We missed the fever in this case and overlooked the idiosyncratic reaction until the 8th cycle. The patient was given diclofenac for fever control at the 9th and 10th cycles.

Patients who develop mild to moderate hypersensitivity to oxaliplatin can be pretreated with steroids and antihistamine, whereas patients who develop severe reactions are unlikely to tolerate any further oxaliplatin therapy (1). Increasing the infusion duration up to 6 hours is recommended for non-life-threatening reactions (3). Treatment should be discontinued for all cases of severe hypersensitivity to oxaliplatin. In such cases, initiation of a desensitization protocol or replacement by other regimens may be considered (6).

We are apt to overlook hypersensitivity reactions to oxaliplatin that show mild symptoms such as fever. Although the incidence of hypersensitivity reactions is low, it is important to carefully observe the development of anaphylactic and idiosyncratic reactions after administering oxaliplatin.

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