Original Article

Incidence and Risk of Oxaliplatin-Induced Hypersensitivity in Patients with Asymptomatic Prior Exposure: A Prospective Observational Study

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What is already known about this topic? The wide use of oxaliplatin in clinical practice has led to an increased incidence of oxaliplatin-induced hypersensitivity reactions (HSRs).

What does this article add to our knowledge? In this prospective study, we observed that patients with previous exposure to oxaliplatin experienced earlier HSR onset and more severe and frequent HSR episodes. A history of asymptomatic exposure to oxaliplatin and a longer oxaliplatin-free interval were independent risk factors for HSRs.

How does this study impact current management guidelines? Clinicians should pay attention to the risk of oxaliplatin HSRs among patients with a history of asymptomatic exposure to oxaliplatin, especially if re-exposure occurs after an oxaliplatin-free interval of more than 3 years.

BACKGROUND: Oxaliplatin-related hypersensitivity reactions (HSRs), which can be life threatening, have introduced a dilemma regarding the use of chemotherapeutic agents. Because repeated exposure to oxaliplatin may increase the risk of sensitization, patients with a history of prior asymptomatic exposure require risk-stratified care.

OBJECTIVE: This study aimed to elucidate the incidence and risk of oxaliplatin HSRs in patients with a history of asymptomatic prior exposure.

METHODS: We performed a prospective observational study of patients who completed oxaliplatin-based chemotherapy between March 2013 and January 2015. Prior exposure to oxaliplatin, the oxaliplatin-free interval, reaction severity, eosinophil counts, and premedication were reviewed to assess the risk factors.

RESULTS: A total of 793 patients were enrolled, among whom 148 (18.7%) experienced an HSR. The HSR incidence was 15.2% among oxaliplatin-naive patients but increased to 31.9% among those with a history of asymptomatic exposure and 75.0% among those with a history of oxaliplatin HSRs during the previous exposure, despite prophylaxis. The mean HSR onset cycle was earliest in the previous HSR group, followed by the previous asymptomatic exposure and nonexposure groups. The HSR severity also differed according to the previous exposure history and HSRs. In the multivariate analysis, prior exposure to oxaliplatin (odds ratio [OR], 3.78; 95% confidence interval [CI], 2.46-5.79) and a longer oxaliplatin-free interval (≥36 months; OR, 4.85; 95% CI, 1.60-14.37) were independent risk factors for HSRs.

CONCLUSIONS: Previous exposure to oxaliplatin is a risk factor for earlier HSR onset and more severe and frequent HSR episodes, even if prior therapy was well tolerated. © **2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;■:■-■)**

Key words: *Oxaliplatin; Hypersensitivity; Drug hypersensitivity; Prospective studies*

Oxaliplatin, a third-generation platinum agent, is a standard treatment option for gastrointestinal malignancies that is usually administered in combination with fluorouracil and leucovorin (FOLFOX regimen) for colorectal cancer[1] or with capecitabine (XELOX regimen) for advanced gastric or colorectal cancer.[2,3] However, oxaliplatin-induced hypersensitivity reactions (HSRs) are reported in 8.9% to 24.3% of cases, and are severe in approximately 1% to 3% of cases.[4-7] Oxaliplatin HSRs range in severity from mild pruritus or urticaria to a fatal anaphylactic reaction.[8,9] Therefore, the precise prediction and optimal management of HSRs are clinically important for patients treated with oxaliplatin.

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Abbreviations used
OR- Odds ratio
CI- Confidence interval
HSR- Hypersensitivity reaction
FOLFOX- Folinic acid, fluorouracil, and oxaliplatin
XELOX- Capecitabine and oxaliplatin

Currently, the risk of re-exposure to oxaliplatin is increasing because gastrointestinal malignancies have increased along with population aging, and advances in medical technology have improved the survival rates of patients with cancer. Cyclic exposure to oxaliplatin increases the risk of sensitization and specific IgE production[10]; however, the former usually occurs without symptom development (ie, silent sensitization).[11] If sensitized patients are re-exposed to oxaliplatin, however, allergic symptoms will eventually manifest. Therefore, oxaliplatin HSR risk stratification should be performed to establish an individualized optimal strategy for high-risk patients who were previously exposed to oxaliplatin.

Herein, we describe a prospective observational study of patients who received oxaliplatin-based chemotherapy. In this study, we assessed the incidence, severity, and risk factors of oxaliplatin HSRs according to the previous oxaliplatin exposure status.

METHODS

Patients

A total of 793 patients who underwent FOLFOX or XELOX chemotherapy were recruited among patients who began and completed an oxaliplatin-based chemotherapy regimen between March 2013 and January 2015 at Seoul National University Hospital. Institutional review board approval was obtained for this study (IRB No.: 1301-118-461), and all patients provided written informed consent to participate in this research.

The patients' demographic data, type of cancer, previous history of oxaliplatin exposure, purpose of chemotherapy, and premedication use were thoroughly reviewed by pharmacovigilance nurses. The occurrence of an HSR and its clinical manifestations were investigated by phone interviews 1 day after oxaliplatin injections, as well as through a complete review of the medical records. HSR severity was evaluated according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0 (CTCAE).[10]

The study patients were divided into 3 subgroups according to their history of previous oxaliplatin exposure or HSRs: group 1 comprised oxaliplatin-naive patients with no history of oxaliplatin exposure, group 2 those with previous asymptomatic exposure to oxaliplatin, and group 3 those with a history of oxaliplatin-induced HSRs during a previous exposure (Figure 1).

Oxaliplatin-containing chemotherapy regimen

The following protocols were used to provide either adjuvant or palliative treatment for gastric cancer and colorectal cancer. FOLFOX comprised biweekly oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, and 5-FU 1000 mg/m^2. XELOX comprised oxaliplatin 130 mg/m^2 and capecitabine 4000 mg/m^2 every 3 weeks. During the seventh cycle and thereafter, chlorpheniramine 4 mg, hydrocortisone 100 mg, and an H_2 antagonist were administered as premedication 1 hour before oxaliplatin administration to prevent oxaliplatin-induced HSRs, because it has been widely suggested that an HSR to oxaliplatin occurs mainly after the seventh infusion.[12] If patients experienced moderate-to-severe emesis, dexamethasone 20 mg was additionally administered.

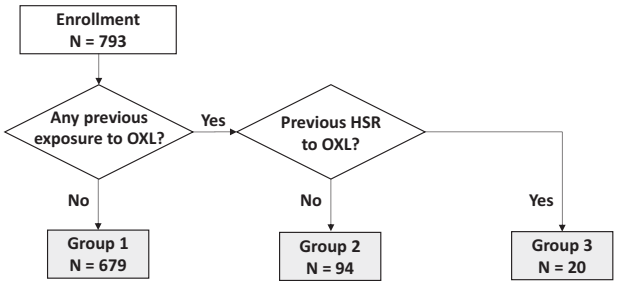

FIGURE 1. Flowchart of study population. *HSR*, Hypersensitivity reaction; *OXL*, oxaliplatin.

Statistical method

The statistical analyses used were χ^2 test or Fisher's exact test for the categorical variables of sex, age group, prior oxaliplatin exposure, cancer type, cancer treatment goal, and HSR. We used a χ^2 test for a linear trend to compare the incidence among 3 groups and a χ^2 test to compare each two groups. Levene's tests of homogeneity of variances were first performed to confirm the normal distribution between groups. A 1-way analysis of variance with the Bonferroni correction was used to compare the mean cycles and oxaliplatin-free intervals among the 3 groups. The independent Student's *t*-test and Mann-Whitney *U* test were performed as appropriate to compare the oxaliplatin-free interval and oxaliplatin cumulative dose according to the occurrence of HSRs.

A multivariate logistic regression model was applied for the risk factor evaluation. Together with sex and age, all variables with a *P* value $< .1$ in the univariate analysis were included as candidate variables in the multiple logistic regression. The results were considered significant if the 2-sided *P* value was $<.05$. The oxaliplatin-free interval times were calculated from the last date of prior exposure to oxaliplatin and were censored for patients who had not developed an HSR at the last follow-up. The oxaliplatin-free interval and HSR were assessed using the Kaplan-Meier method. Statistical analyses were performed using SPSS software (version 23.0; SPSS, Chicago, Ill).

RESULTS

Study subjects

The patients' baseline characteristics are listed in Table I. The mean age was 59.0 (±10.8) years, and 481 (60.7%) were male. Colorectal cancer (67.0%) was the most common therapeutic indication, followed by gastric cancer (31.9%) and pancreatic or liver cancer (1.0%). Oxaliplatin was administered to 464 patients (58.5%) for adjuvant chemotherapy and 329 patients (41.5%) for palliative treatment. One hundred fourteen patients (34.7%) had been exposed to oxaliplatin previously, including 20 patients with a history of previous oxaliplatin HSRs. Regarding the chemotherapy regimen, 63.7% of patients received XELOX and 36.1% received FOLFOX.

Oxaliplatin HSR incidence and severity

The overall incidence of an HSR was 18.7%. Among oxaliplatin-naive patients (group 1), only 15.2% experienced an