Skin Test Protocol for the Prevention of Hypersensitivity Reactions to Oxaliplatin

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Abstract. Background/Aim: Several hypersensitivity reactions (HSRs) to oxaliplatin have been reported. Presently, there is no reliable way to predict the development of this adverse reaction. The aim of the present study was to evaluate the reliability of skin tests in the detection of patients at risk of developing HSRs to oxaliplatin. Patients and Methods: Patients under treatment with oxaliplatin underwent the prick test at a concentration of 1 mg/ml and, if negative, intradermal injection at a concentration of 0.1 mg/ml, one hour before each course of oxaliplatin, starting from the second administration. Results: A group of 101 patients were submitted to skin tests: two were positive, whereas five developed HSR despite negative tests (false-negative rate: 5.05%). These patients underwent desensitization, which permitted to conclude the planned schedule in five cases. Conclusion: A negative skin test to oxaliplatin has a good reliability in predicting HSRs. We suggest performing tests only in patients that have received at least five courses of oxaliplatin.

Oxaliplatin is a third-generation platinum compound used in combination with other cytostatics, such as 5-fluorouracil, capecitabine, and gemcitabine, for the treatment of many types of cancers, namely, colorectal (adjuvant and metastatic), gastric, pancreatic, biliary tract, and ovarian, and more rarely, for melanoma, non-Hodgkin’s lymphoma, non–small cell lung, and head and neck cancer (1-3). The use of this chemotherapeutic drug has increased in a substantial degree in recent years because of its efficacy and manageability; the main and peculiar toxicities are cold-sensitive dysesthesia and peripheral neurotoxicity. Oxaliplatin, like other platinum compounds cisplatin and carboplatin, provokes hypersensitivity reactions (HSRs) that are usually unpredictable and often not severe. Fewer than 1% of allergic reactions are life-threatening although deaths have been reported (4). The incidence of the reactions described ranges between 0.5% and 25% of those undergoing treatment. The reactions are often of grade 1 to 2 in severity according to the National Cancer Institute classification (5) and cause itching and erythema, especially on the palms and soles; the symptoms can develop either during the infusion of the drug or during the next few hours (6). Treatment of these mild reactions is based on oral anti-histamines and steroids. More severe reactions (grade 3) are characterized by generalized urticaria, facial swelling, diffuse erythroderma, and bronchospasm, and can evolve in about 1% to anaphylaxis (7). These reactions appear on average at the seventh to eighth administration, 5 to 10 min after the beginning of chemotherapy, and have to be treated with intravenous anti-histamines and steroids and, in some cases, with epinephrine (6). In most patients, the first reaction is mild and becomes severe at re-challenge. Therefore, before beginning of new treatment, it is very important to ask the patients how well they tolerated the previous infusion. Therapeutic strategies to reduce HSRs to oxaliplatin, such as pre-medication with anti-histamines and steroids or slowing infusion rates, or both, are frequently not effective, so oncologists are forced to substitute this anti-neoplastic agent with other, often less effective, chemotherapy. Keeping this in mind, in recent years, several authors have tried to develop rapid desensitization protocols that allow temporary tolerization to HSR-induced chemotherapeutic drugs. Results were encouraging and most patients were able to complete the planned schedule of chemotherapy (8-10). The role of platinum-specific IgE antibodies in the development of hypersensitivity reactions to oxaliplatin is well-documented (11, 12). The reactions present after several courses of chemotherapy, suggesting that sensitization to the drug occurs. The early onset of clinical manifestations during the infusion of therapy is compatible with IgE-mediated reactions and a positive result of skin test to oxaliplatin underlines an IgE-mediated mechanism. Indeed, skin tests are sensitive for the diagnosis of HSRs to oxaliplatin, with a sensitivity ranging
from 75% to 100% (13-15). Most reliable results are obtained with an intradermal test, when the reaction has developed during the infusion of oxaliplatin, or within 2 h of the end of therapy (16). Cross-reactivity to other platinum-containing drugs can occur. Leguy-Seguin et al. observed positive results of skin tests for oxaliplatin and carboplatin in 3 patients who were allergic to oxaliplatin and were never exposed to carboplatin (16). On the other hand, eight patients with allergy tolerated another platinum compound, which gave a negative result in skin tests. Similar results were obtained by other investigators (17). Unfortunately, the efficacy of oxaliplatin is comparable to that of other platinum salts only for the treatment of few types of cancer, for example, pancreatic or ovarian cancer, whereas it is much higher for other types of cancer, especially colorectal cancer, where it is not replaceable. As previously stated, HSRs to chemotherapeutic drugs are presently unpredictable and risk factors for their development still are not identified. For those reasons some authors tried to evaluate the role of skin test in the prevention of HSRs to platinum salts. In this regard Markman et al. showed that intradermal skin test with 0.02 ml of undiluted carboplatin performed 30 min before chemotherapy was able to identify patients who could receive carboplatin safely with a negative predictive value of 98.5% (18). In another study, the negative predictive value of skin tests carried out before carboplatin administration was 91.5% (19).

The first aim of our prospective study was to investigate if skin tests with oxaliplatin administered before the course of chemotherapy could help clinicians identify patients at risk of developing HSRs during or after the end of oxaliplatin-based chemotherapy. The secondary aim was the evaluation of the feasibility and safety of a desensitization protocol in these with positive skin tests or with HSRs to oxaliplatin.

**Patients and Methods**

The study was approved by the Ethical Committee of the Hospital centre C.Poma, Mantua (approval number 145/2009). In the period between October 2009-October 2011 all the patients treated with OHP in our Institution were informed about the protocol and subsequently enrolled in the study after informed consent. One hour before the infusion of oxaliplatin, patients underwent skin tests consisting of a prick test with a solution of oxaliplatin at the concentration of 1 mg/ml, starting from the second course of therapy. Where the prick test was found to be negative, skin tests were repeated with an intradermal injection of 0.02 ml of oxaliplatin solution at the concentration of 0.1 mg/ml. These concentrations were obtained with the dilution of the commercial drug Eloxatin (Sanofi-Aventis, Paris, France) in physiological saline solution and had been standardized in a previous study (13). Each test was read and evaluated 15, 20, and 30 min after administration. In conformity with the recommendations of the European Academy of Allergy and Clinical Immunology, the prick test was considered positive when the cutaneous response was a wheal of at least 3 mm with a surrounding flare, while the intradermal test was considered positive with a wheal of at least 5 mm with a surrounding flare (20). If tests were negative, oxaliplatin was administered intravenously in 2 h, after pre-medication with ondansetron 5 mg in 100 ml of NaCl (0.9%) infused in 15 min, in accordance with the customary modalities performed in our Center. The patients were then investigated again during the following days (24 and 72 h after the test) to determine whether there were any delayed reactions.

Patients with positive skin tests and those that suffered symptoms compatible with immediate reactions during the infusion of oxaliplatin underwent desensitization according to the 12-step protocol previously described by Castells et al. (8).

A database of the patients included in the study was constructed. Data regarding the patient, namely name, age, gender, familiar and personal history of atopy, cancer characteristics (type, stage, site of metastases) and schedule of chemotherapy were collected. Severity of HSRs was classified according to NCI toxicity criteria (5).

**Results**

A total of 101 patients were enrolled (69 male’s and 32 female’s), with a median age of 65.5 years. A personal history of atopy was recorded in 12 cases (12%). The neoplasms treated were: colorectal cancer (n=81), pancreas and biliary tract (n=16) and stomach cancer (n=4); 48 patients were disease-free, 43 presented metastases and the other 10 had locally advanced cancer.

Oxaliplatin was administered with 5-fluorouracil (FOLFIRI-4) in 53 cases, with 5-fluorouracil-plus-bevacizumab in 16, with capecitabine (XELOX) in 16 patients and the remaining 16 were treated with gemcitabine (GEMOX).

A total of 836 skin tests were performed (8 per patient on the average). No serious adverse effects caused by skin tests were observed. All the prick tests were negative, whereas two patients had a positive intradermal test. The first patient, a 61 year-old man with a resected colon cancer, had a positive test before the sixth course of therapy. In the second case, a woman with resected colon cancer, a positive intradermal test was found before the seventh cycle of chemotherapy. On the other hand, as regards the 99 patients with negative skin tests, five developed HSRs during infusion of oxaliplatin, leading to a 5.05% false-negative rate for skin tests. The average number of courses of oxaliplatin given in this group of patients was 7 (range=5-8). Table I describes the characteristics of the patients with HSRs.

Overall, 7/101 patients (7%) were allergic to oxaliplatin treatment. We evaluated several variables (age, sex, history of atopy, number of doses of oxaliplatin received, concomitant therapies) with the aim of detecting their impact on the occurrence of HSRs, but none was associated with this type of adverse reaction.

The five patients with HSRs to oxaliplatin and the two with the positive intradermal test underwent the desensitization protocol. All but two patients concluded the planned schedule of chemotherapy; the total number of desensitizations performed was 29. Regarding the two patients in whom therapy was interrupted, the first was the male with a positive skin test,
who developed urticaria and dyspnoea during the twelfth step of the first desensitization. The therapy was then stopped because the patient revoked his consent to finish the procedure after the reaction. In the other case, in which HSR occurred during the eighth cycle despite negative skin tests, the first desensitization was performed without reactions, but the therapy was subsequently suspended due to progression of disease (pancreatic cancer).

No reactions occurred in 21/29 (83%) desensitizations and mild reactions were observed in 3/29 (10%), including the woman with positive intradermal test. Grade 3 reactions developed in two patients who, however, concluded the planned schedule of therapy. All the reactions appeared during the administration of solution C. In brief, the drug is prepared in 3 solutions: the first contains a 100-fold dilution of the final target concentration; the second, a 10-fold dilution; while the third is obtained by subtracting from the final total dose the cumulative dose presented in the first 2 solutions. Each solution is administered in 4 steps at increasing infusion rates (steps 9-12). All the patients presented the adverse reaction during the first round of desensitization.

**Discussion**

It has been known for many years that platinum derivatives can cause HSRs in workers exposed to them by inhalation (21). In addition, the platinum compounds cisplatin, carboplatin and oxaliplatin utilised in clinical practice for the treatment of a number of types of cancer can lead to type-1 hypersensitivity reactions. As far as oxaliplatin is concerned, reports of HSRs, even very severe ones, are increasing (4, 6, 7). The clinical pictures reported typical of IgE-mediated reactions, occur during the infusion of the drug and usually arise after several infusions of oxaliplatin, on average seven, which clearly reflects the need for repeated exposure to the drug to induce an allergic immune response. Moreover, skin tests with platinum compounds were positive in several studies (11-16), confirming the IgE-mediated pathogenesis of several cases of allergic reaction. HSRs to platinum salts are actually unpredictable and there are no factors able to identify patients at risk of developing allergic reactions.

In recent years, Markman *et al.* evaluated the role of skin tests for the prediction of HSRs to carboplatin, performing an intradermal test with the solution of the drug prepared for the treatment 30 min before chemotherapy, in 126 patients who had previously received more than six doses of the drug. The total number of skin tests was 717 (median of four per patient) and the authors reported 10 negative tests followed by mild-to-moderate HSRs (1.5% false-negative rate), demonstrating an important role of skin tests in the prediction of severe HSRs to carboplatin (18). In another study Gomez *et al.* carried out an intradermal test with a solution of carboplatin on 54 patients undergoing carboplatin-based re-treatment for gynaecological cancer (19). Seven patients had positive skin tests whereas HSRs, not severe however, occurred in four patients despite negative intradermal test (8.5% false-negative rate). The authors concluded that skin tests were not very reliable in the prediction of carboplatin-induced HSRs. In our study we analyzed 101 consecutive patients who received an oxaliplatin-based chemotherapy by performing prick and intradermal tests with this drug, one hour before the administration of oxaliplatin. We recorded a good false-negative rate (5.05%) of skin tests. In addition, the variables analyzed (age, sex, history of atopy, number of doses of oxaliplatin received, concomitant therapies) were not correlated with the two positive skin tests nor the five HSRs developed during the study. In this regard, HSRs observed were all mild but one, a grade 3 reaction developed during the seventh infusion of oxaliplatin in a 52-year-old man with a relapse of colorectal cancer. In our opinion, skin tests seem to predict for the absence of a severe HSR on the subsequent drug infusion with a good reliability. In clinical practice, we suggest that screening with intradermal tests must be started from the fifth cycle of oxaliplatin.

As far as desensitization is concerned, many studies have been published in recent years, showing good results in the treatment of patients with HSRs to several chemotherapeutic drugs, including monoclonal antibodies (8-10). Analysing platinum salts, Castells *et al.* (8) and Feldweg *et al.* (9) demonstrated that desensitization to these anti-neoplastic agents was safe and effective in 31 and 60 patients respectively who were allergic to carboplatin. Regarding the role of desensitization in oxaliplatin-induced HSRs, the greatest number of patients was very recently evaluated by Madrigal-Burgaleta *et al.* (12). In their study, 10 patients with severe HSRs to oxaliplatin received the drug with a 10-step protocol, achieving complete administration of the planned schedule of chemotherapy in all cases. In our study, we carried-out desensitization in the two patients with positive intradermal test and in the five cases of HSRs. The 12-step procedure subsequently allowed successful administration of oxaliplatin-based regimen of chemotherapy in 5 cases. However, if we exclude the patient in whom therapy was stopped because of progression of pancreatic cancer, the desensitization program allowed planned therapy to be completed in 6 patients, confirming the efficacy and safety of this methodology.
In conclusion, skin tests with oxaliplatin have a good reliability in predicting HSRs to this chemotherapeutic drug. In our opinion, the prick test is not useful in this setting, hence it is probably more convenient to carry-out only intradermal injection at a concentration of 0.1 mg/ml of oxaliplatin. Moreover, we recommend not performing the test in all patients, but only in those who had received at least five courses of oxaliplatin. More studies are necessary to possibly detect other factors correlated with positivity of skin tests.

Regarding the 12-step desensitization procedure, also our study confirms its efficacy and safety in the administration of oxaliplatin in patients with previous HSRs. However, we stress out that desensitization is a complicated and potentially very dangerous methodology and should only be administered in very selected cases by expert health personnel.

References


