Hypersensitivity reactions to oxaliplatin: experience in a single institute


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Background: A rising incidence of hypersensitivity reactions to oxaliplatin has been observed as a result of increasing clinical use. Epidemiological and clinical features of these reactions are reviewed.

Patients and methods: Records of patients treated with a modified FOLFOX regimen from March 1999 to March 2004 were reviewed.

Results: One hundred and eighty patients were identified. Twenty-seven patients (15%) have been labelled as allergic to oxaliplatin, the proportion being higher among those receiving oxaliplatin in palliative second-line or above settings (19.6%) than in adjuvant or palliative first-line settings (10.2%). Some 2.2% of them developed grade 3–4 reactions. The reactions occurred after a mean (± SD) of 8.5 (± 4.2) cycles (range 1–18). Among the 14 patients re-exposed to oxaliplatin, four (28.6%) developed hypersensitivity reaction, in two of whom (14.3%) reactions were grade 3–4 in severity.

Conclusions: The risk of developing hypersensitivity reactions in patients receiving oxaliplatin should not be underestimated. The risk of developing potentially life-threatening hypersensitivity reactions should be explained to patients in the context of the potential benefits of such therapy. Patients receiving oxaliplatin infusion should be closely monitored. Once a patient develops hypersensitivity reaction to oxaliplatin, re-exposure should only be considered if the reaction is mild and there has been documented clinical benefit from previous doses of this agent.

Key words: chemotherapy, hypersensitivity, oxaliplatin

introduction

Oxaliplatin, a third-generation organoplatinum with significant activity in colorectal cancer, is now being increasingly used in daily clinical practice. In Queen Mary Hospital, it was first employed in the palliative setting in patients with metastatic colorectal cancer, but based on the recent data from the MOSAIC trial [1], it is presently also given as an adjuvant treatment for selected patients with Dukes’ C colorectal cancer, subject to clinical indications and patient’s preference. Oxaliplatin has also been used in the Queen Mary Hospital in combination with capecitabine in preoperative chemoirradiation for locally advanced rectal cancer in a trial setting, as reported in the World Congress on Gastrointestinal Cancer in Barcelona in June 2004 [2]. Apart from colorectal cancers, oxaliplatin has shown promising activity in other malignancies as well, and patients with cancer of pancreas and stomach have also received this agent in our department.

Hypersensitivity reactions to platinum derivatives have been described in the literature, with variable incidence ranging from ~5% [3] to as high as 27% [4]. Being a platinum derivative, it is not surprising that patients receiving oxaliplatin can develop hypersensitivity reactions, as similar reactions towards carboplatin have been reported previously [4]. With increasing use of oxaliplatin in clinical practice, we are now encountering an increasing incidence of suspected hypersensitivity reactions, the clinical presentation and severity of which can be highly variable.

The aim of this study was to examine the epidemiological and clinical features of hypersensitivity reactions to oxaliplatin in patients treated with this agent in the Department of Clinical Oncology, Queen Mary Hospital, in order to provide some useful clinical information for the management of patients receiving oxaliplatin infusion.

materials and methods

Patients who were given chemotherapy using a modified FOLFOX VI regimen with a higher dose of oxaliplatin (oxaliplatin 100 mg/m² day 1, leucovorin 200 mg/m² days 1 and 2, 5-fluorouracil 1500–2000 mg/m² days 1 and 2 every 2 weeks) in the Department of Clinical Oncology, Queen Mary Hospital, between March 1999 and March 2004 have been identified and their records reviewed. Patients using oxaliplatin in other regimens, which constituted only ~10% of all patients receiving oxaliplatin in our hospital, have been excluded from the current analysis for the sake of simplicity.

results

We identified 180 patients who received modified FOLFOX regimen during the stated period. All except two suffered from colorectal cancer. None of them had received other platinum
agents previously. Among these 180 patients, 27 were labelled as ‘allergic’ to oxaliplatin, accounting for 15% of all patients who received FOLFOX. More than half (55.6%) of the reactions occurred within the first hour. These reactions usually occurred after a mean (± SD) of 8.5 (± 4.2) cycles (median nine cycles); however, the range is wide, varying from one to 18 cycles.

The data on patients who developed hypersensitivity reactions after receiving FOLFOX are presented in Table 1. Of all patients receiving FOLFOX, 2.2% developed grade 3–4 hypersensitivity reactions (as defined in the Common Terminology Criteria for Adverse Events v3.0 [3]). However, if we divide our patients into two groups, those receiving FOLFOX in an adjuvant or palliative first-line setting and those in a palliative second-line or above setting (meaning that these patients have been more heavily pretreated with other agents, >80% of which were irinotecan combination regimens, prior to oxaliplatin), we find that those patients who had been previously exposed to other agents seemed to develop hypersensitivity reactions almost twice as often (19.6% versus 10.2%) as the previously untreated patients.

Table 2 summarizes the various presentations of the hypersensitivity reactions. Patients most commonly developed rash, itchiness, fever/chills/rigor and flushing, as in other hypersensitivity reactions. Other manifestations are also possible, including the more severe such as hypotension, oxygen desaturation and full-blown anaphylactic reactions.

Among the 27 patients with hypersensitivity reactions, we have re-challenged 14 of those who developed grade 1–2 reactions (Table 3). All received steroid and chlorpheniramine as premedication, but the doses and routes were not uniform, as there were no standard premedication regimens for prevention of hypersensitivity reactions towards oxaliplatin at that time. Both oral and intravenous routes were used. Four of those patients re-challenged developed hypersensitivity reactions again, two of which were of grade 3–4 in severity. This translates into 28.6% for all reactions and 14.3% for grade 3–4 reactions, much higher than those suffering their first episode of hypersensitivity reaction.

**Discussion**

Are our data similar to or very different from those observed by other investigators? From our literature review (Table 4), the percentages of hypersensitivity reactions quoted in different studies range from 8% to 20%, but are usually around 10% to 12%. Our data are thus probably not very different from those reported in the literature. The percentage of grade 3–4 reactions is also similar, in the order of 1–2%. However, our observation of higher risk of developing hypersensitivity reactions in heavily pretreated patients is not reported in other studies. According to information from the official website of Eloxatin [10], the percentage of patients developing hypersensitivity reactions in first- and second-line settings seem to be more or less the same.

It seems that the overall incidence of hypersensitivity reactions to oxaliplatin is similar across different studies, probably around 10–15%. However, we have observed a higher incidence of hypersensitivity reactions in patients who have been exposed to other agents (over 80% of which being irinotecan combination regimens), a finding not reported in other studies. None of these patients had been exposed to platinum previously. As there has been no reported cross-reactivity between irinotecan and oxaliplatin in the medical literature as far as we know, further investigations are probably necessary to determine whether such a difference is genuine. We also observe that if patients develop a hypersensitivity reaction to oxaliplatin, however mild it is, they are more prone to develop hypersensitivity reactions upon rechallenge, even with steroid and chlorpheniramine cover, and there seems to be a higher risk of grade 3–4 reactions. If this is proven to be genuine, it is clinically significant and one has to consider very carefully the therapeutic ratio before re-challenging patients who are known to have had hypersensitivity reactions towards oxaliplatin.

Our review of data does have limitations. First of all, being a retrospective review, it is very difficult to confirm now whether those observed reactions are genuine hypersensitivity reactions or whether those reactions developed truly as a result of oxaliplatin infusion only, although the temporal relationship between infusion and onset of reaction is suggestive. Therefore, it is possible that the risk may have been overestimated. We can also argue the other way round, that is, some mild reactions may have been missed resulting in underestimation. It has also been discussed in the literature that patients can develop ‘idiosyncratic reactions’ (defined as abnormal reactions to a drug that are not antibody related, the onset of which may be delayed instead of immediate [12]) towards oxaliplatin, which

**Table 2. Presentation of hypersensitivity reactions to oxaliplatin**

<table>
<thead>
<tr>
<th>Presentation</th>
<th>No. of patients (%)</th>
</tr>
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<tbody>
<tr>
<td>Rash</td>
<td>12 (44.4)</td>
</tr>
<tr>
<td>Itchiness</td>
<td>9 (33.3)</td>
</tr>
<tr>
<td>Fever/chills/rigor</td>
<td>8 (29.6)</td>
</tr>
<tr>
<td>Flushing</td>
<td>8 (29.6)</td>
</tr>
<tr>
<td>Chest tightness/discomfort</td>
<td>5 (18.5)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4 (14.8)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>4 (14.8)</td>
</tr>
<tr>
<td>Abdominal pain/cramps</td>
<td>4 (14.8)</td>
</tr>
<tr>
<td>Diarrhea/nausea/vomiting</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Blocked nose/runny eyes/conjunctival congestion</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Sweating</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Peritoneal edema</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Desaturation</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>1 (3.7)</td>
</tr>
</tbody>
</table>

Total number of patients = 27 (patients can have more than one presentation each).
are not true hypersensitivity reactions. Clinically, however, it is probably difficult to differentiate between the two. There is also no standard premedication for re-exposure to oxaliplatin after prior hypersensitivity reaction, making an accurate estimation of risk of re-exposure difficult. It has also been mentioned in isolated case reports, e.g. Gammon et al. 2004 [13], that a desensitisation schedule can be attempted, although this is probably not a universally adopted approach.

**Conclusions**

The risk of developing hypersensitivity reactions in patients receiving oxaliplatin should not be underestimated. In our observation, approximately 10–15% of the patients receiving oxaliplatin will develop hypersensitivity reactions, often during the seventh to ninth cycle of the FOLFOX regimen, but they can actually occur during any cycle. The observation of a higher risk of reaction in patients previously treated with other regimens is intriguing, and given its significance, further investigation is warranted. Most of these reactions are mild to moderate in severity but life-threatening events are possible, especially for those who are known to have had hypersensitivity reactions towards oxaliplatin (even with premedications).

In response to the findings in this analysis, several amendments in practice have been adopted in the Department of Clinical Oncology, Queen Mary Hospital. The risk of developing hypersensitivity reactions, which can be potentially life-threatening, will be clearly explained to all subjects who are going to receive combination chemotherapy involving oxaliplatin. Patients receiving oxaliplatin are closely monitored and instructed to report any symptoms that possibly reflect hypersensitivity reactions immediately. Once a patient develops hypersensitivity reaction to oxaliplatin, re-exposure will be considered only if the reaction is mild and there has been documented clinical benefit from previous doses.

The clinical benefits of oxaliplatin in the treatment of cancer are gaining momentum as more evidence emerges from the medical literature. Anticipating an increase in use of oxaliplatin in clinical practice, however, a careful balance of risk and benefit has to be considered for the individual patient. Close monitoring should be applied to all subjects, until full elucidation of the risk factors precipitating such reactions are known.

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**References**