Adverse reactions to oxaliplatin: a retrospective study of 25 patients treated in one institution

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We reviewed the records of 25 colon cancer patients consecutively treated with an oxaliplatin-containing regimen. We differentiated between hypersensitivity reactions and pain reactions due to oxaliplatin. The patients did not receive preventive pre-medication. Four patients underwent an adverse reaction. Three patients fulfilled the criteria of a hypersensitivity reaction with tachycardia, chills and hyperhidrosis. In addition, two patients suffered from severe abdominal and chest pain. Reactions occurred during or shortly after the oxaliplatin infusion. All patients recovered under symptomatic therapy. After reacting for the first time, pre-medication was applied prior to the oxaliplatin infusion. However, due to further reactions, the treatment protocol had to be changed in all cases into a regimen not containing oxaliplatin. We conclude that adverse reactions are relatively frequent toxic side-effects of oxaliplatin, mainly in heavily pre-treated patients. Pre-medication was ineffective in preventing further reactions and consequently the treatment regimen had to be changed in all cases. *Anti-Cancer Drugs* 14:731–733 © 2003 Lippincott Williams & Wilkins.

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Introduction

Oxaliplatin is a third-generation platinum derivative, which acts as an alkylating agent on DNA. Its clinical use is mainly established in the therapy of colorectal cancer. In several prospective, multicenter phase II studies oxaliplatin proved its efficacy in patients with colorectal cancer as single agent or in combination with 5-fluorouracil and leucovorin (5-FU/FA) [1–3]. In addition, it has shown activity in various other cancers including pancreatic, ovarian or non-small cell lung cancer [4–6].

Oxaliplatin is considered to be a well-tolerated chemotherapeutic agent with a different toxicity profile than other platinum derivatives. Adverse events described most often are gastrointestinal toxicity, hematologic side-effects and neurotoxicity [7–10]. Hypersensitivity reactions to oxaliplatin characterized by tachycardia, dyspnea, chills or fever have been described sporadically in the literature [11,12]. In the only study published so far, Dold *et al.* [13] reported a frequency of hypersensitivity reactions to oxaliplatin of 8%. These reactions were mainly seen in pre-treated patients. Episodes of abdominal pain have been reported so far only under locoregional oxaliplatin therapy [14–16]. To our knowledge, only single reports of patients suffering from abdominal pain under systemic oxaliplatin therapy have been presented. The prevalence of pain reactions occurring under systemic oxaliplatin has not yet been described. Observing severe hypersensitivity and pain reactions in patients treated in our institution led us to investigate the frequency of these incompatibility events.

Consequently, in this retrospective study, we reviewed the records of 25 patients diagnosed with colon carcinoma treated consecutively with an oxaliplatin-containing regimen at the outpatient service of our clinic. Our results suggest that adverse reactions during systemic chemotherapy with oxaliplatin are relatively frequent events, mainly in heavily pre-treated patients.

Patients and methods

In this study the records of 25 patients consecutively treated with oxaliplatin-containing chemotherapies at the outpatient service of the Großhadern Hospital of the Ludwig Maximilians University Munich (male = 21, female = 4) were analyzed. All patients were diagnosed with a metastatic colorectal carcinoma. Median age was 60 years. Different systemic oxaliplatin containing regimens were applied. Twelve patients received the combination of oxaliplatin (85 mg/m^2), 5-FU (24 h, 2000 mg/m^2) and leucovorin (2 h, 500 mg/m^2); 11 patients were treated with oxaliplatin and irinotecan (CPT-11; 30 min, 80 mg/m^2), whereas in two cases oxaliplatin and raltitrexed (Tomudex; 15 min, 3 mg/m^2) were administered. Oxaliplatin was applied as a 2-h infusion. Supportive therapy included a 5-HT_3 antagonist p.o. In

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seven patients, the oxaliplatin-containing regimen was given as first-line therapy, whereas 18 patients were pre-treated with other chemotherapeutic regimens prior. Five of the 18 pre-treated patients (27%) had received oxaliplatin previously, either as hepatic arterial infusion or as part of another systemic regimen. In the 25 patients, a total of 132 oxaliplatin doses was applied.

Adverse reactions to oxaliplatin infusions were differentiated into hypersensitivity reactions and pain reactions. Hypersensitivity reactions in general are classified into four types (immediate type, antibody mediated, immune complex mediated and cell mediated). The pathogenesis of hypersensitivity to chemotherapeutic agents, however, often is not known [17]. Therefore, we defined hypersensitivity to oxaliplatin infusions according to the Common Toxicity Criteria (CTC) by rash, fever, dyspnea and symptoms of anaphylaxis [18,19]. Pain episodes were defined as chest or abdominal pain and also classified according to the CTC [18,19].

Results

We analyzed the frequency of hypersensitivity and pain reactions to oxaliplatin in 25 patients with the diagnosis of colorectal carcinoma who were treated with different systemic oxaliplatin-containing regimens. Hypersensitivity reactions were defined according to the CTC by rash, fever, dyspnea and symptoms of anaphylaxis [18,19]. Pain episodes were defined as chest or abdominal pain and also classified according to the CTC [18,19].

In our series, four of the 25 patients suffered from hypersensitivity and pain reactions. Three patients underwent a hypersensitivity reaction with tachycardia, which was observed in all cases, fever and hyperhidrosis. No skin rash was observed. However, one of the patients also suffered from severe grade 3 abdominal and chest pain according to the CTC. In addition, a similar episode was observed in another patient. Consequently, pain reactions occurred in two of 25 treated patients. All reactions occurred during or shortly after the infusion of oxaliplatin. All patients recovered quickly under symptomatic therapy and could be discharged the same day. Long-term adverse effects in these patients were not observed. Altogether, three different oxaliplatin treatment regimens were applied. The absolute oxaliplatin dose given varied between 80 and 250 mg. No correlation between dosage and occurrence of reactions could be found. Preventive pre-medication such as diphenhydramine, acetaminophen or dexamethasone was not applied in any instance.

All patients undergoing an adverse event had received oxaliplatin infusions prior to the reaction. The median number of doses administered prior was 4. Reactions occurred only in patients who had received chemotherapy before. Adverse effects were not seen in the seven patients that were previously untreated and received oxaliplatin as first-line therapy. Most interestingly, three of the four patients showing adverse reactions had received oxaliplatin prior as part of other treatment schedules (one loco-regional regimen and two systemic regimens). Altogether, only five of the 25 patients had received oxaliplatin in another regimen before. Consequently, three out of these five patients reacted to newly applied oxaliplatin (Table 1).

Table 1 Patient characteristics

No. of patients	25
Male : female ratio	21:4
Diagnosis	metastatic colorectal carcinoma ($n = 25$)
Median age [years (range)]	60 (42–77)
Median no. of prior treatments (range)	1 (0–4)
Median no. of courses prior to reaction (range)	4 (1–4)

In two patients, oxaliplatin was administered again after the first reaction. However, pre-medication with diphenhydramine and acetaminophen was ineffective in preventing further reactions to oxaliplatin infusions. Consequently, in all four patients the treatment protocol had to be changed into a regimen not containing oxaliplatin. No further reactions occurred after terminating the application of oxaliplatin.

Discussion

Oxaliplatin is a well-tolerated chemotherapeutic agent with established anti-tumor activity in colorectal carcinoma and other tumors [1–3]. Hypersensitivity reactions, which can be potentially life threatening have been described in the literature mainly as case reports [11,12]. The only study published so far by Dold *et al.* [13] reported a frequency of hypersensitivity reactions of 8%.

The scarcity of evaluable data led us to determine the frequency of hypersensitivity reactions to systemic oxaliplatin in patients with colorectal carcinoma. In our study, three patients underwent a hypersensitivity reaction to oxaliplatin, confirming the results of Dold *et al.* Reactions occurred after applying a median of 4 doses of oxaliplatin, which also confirmed the results of Dold *et al.* In addition, two patients in our series suffered from severe grade 3 chest or abdominal pain according to the CTC. Abdominal pain was previously described as a common side-effect of loco-regional oxaliplatin therapy [14–16]. However, this important side-effect has not yet been published in a larger series of patients receiving systemic oxaliplatin therapy. Interestingly, in the study of Dold *et al.*, pain reactions to systemic oxaliplatin were not documented. On the basis of our data, however, we concluded that oxaliplatin-induced pain reactions are

relatively frequent. The mechanisms leading to severe pain are currently unknown. However, we observed that the frequency of abdominal pain in patients receiving oxaliplatin as hepatic arterial infusion decreased significantly after pre-medication with the calcium antagonist nifedipine was initiated (unpublished data). Therefore, a possible mechanism of pain reactions might be the interaction of oxaliplatin with calcium channels.

Patients reacting to oxaliplatin were all prior treated with at least one other treatment regimen. None of the patients in our series who received oxaliplatin as first-line therapy ($n = 7$) reacted. The absolute applied oxaliplatin dose varied between 80 and 250 mg. No correlation between dosage and occurrence of reactions could be found. Three of the four patients who reacted received prior oxaliplatin-containing chemotherapy. Therefore, we further concluded that incompatibility reactions to systemic oxaliplatin occurs mainly in heavily pre-treated patients independent of the applied dose. Additionally, a prior therapy with systemic or loco-regional oxaliplatin seems to be a major risk factor for developing an incompatibility reaction. Therefore, we consider that the different incidences of pain reactions to oxaliplatin between our study and the study of Dold *et al.* might be explained by the number and type of prior treatments.

In our series, preventive pre-medication with diphenhydramine and acetaminophen was ineffective in preventing further reactions. The treatment protocol had to be changed in each patient. No further reactions occurred after terminating the application of the oxaliplatin-containing chemotherapy, clearly indicating the adverse reactions being triggered by oxaliplatin. However, in contrast, Dold *et al.* reported that pre-medication containing dexamethasone, cimetidine, diphenhydramine, acetaminophen and granisetron was effective in preventing further reactions. Consequently, we conclude that a pre-medication regimen containing steroids may be able to prevent reactions to oxaliplatin.

The pathogenesis of the described adverse reactions to oxaliplatin has not yet been elucidated. The study of Tonini *et al.* [20] claimed release of cytokines such as tumor necrosis factor-α or interleukin-6 to be involved. These results have to be confirmed and further studies are necessary to clarify the pathogenesis of these events.

In conclusion, oxaliplatin-induced hypersensitivity and pain reactions are relatively frequent, and occur mainly in pre-treated patients. These reactions normally resolve quickly under symptomatic therapy and long-term adverse effects have not been observed. Steroid pre-medication might fully or partially prevent further reactions, but this needs to be confirmed.

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