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Letter to Editor

A Novel Oxaliplatin Desensitization Protocol: Short, Safe, and Effective

Oxaliplatin, a third-generation platinum containing chemotherapeutic agent, has a key role in the management of colorectal cancer, both in adjuvant and metastatic settings. It also finds use in gastrointestinal primaries of other locations. Although serious hypersensitivities and anaphylaxis to oxaliplatin occur rarely, further treatment is considerably compromised in such situations. In this regard, many desensitization protocols for oxaliplatin have been used in the past to warrant continuation of chemotherapy with the drug. We report a case of a young female with metastatic colorectal cancer who developed a hypersensitivity reaction to oxaliplatin and was successfully desensitized using a modified approach.

A 25-year-old young female, diagnosed with ulcerative colitis, presented with altered bowel habits, weight loss, and bleeding per rectum of 6 months of duration. On evaluation, a sigmoid colonic mass was found extending up to the rectosigmoid junction. Staging revealed metastatic disease. She underwent cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HiPEC) (HiPEC protocol: intraperitoneal: mitomycin C 20 mg, and doxorubicin 20 mg and intravenous: 5FU 600 mg, and leucovorin 30 mg) uneventfully. Postoperative histopathology was signet ring cell adenocarcinoma with pathological stage T4bN1bM1. Subsequently, adjuvant chemotherapy with capecitabine and oxaliplatin (CAPOX), with cycle interval of 21 days, was initiated. The brand of oxaliplatin used in the patient was Dacotin. The patient tolerated the first cycle of CAPOX well and was administered the second cycle as per protocol. However, she developed a Grade 3 (CTCAE common toxicity criteria)[1] hypersensitivity reaction to oxaliplatin after the infusion. She complained of giddiness, dyspnea, sweating, generalized uneasiness, and responded to antihistaminic and corticosteroid injections. During the third cycle of CAPOX, she again developed a similar hypersensitivity reaction to oxaliplatin, and the infusion had to be stopped. Following this, it was planned to desensitize her using a modified oxaliplatin desensitization protocol on an inpatient basis and not in daycare. After assessing fitness for chemotherapy, she received the calculated dose of oxaliplatin divided into five separate infusions of serially increasing concentrations of oxaliplatin. The entire infusion protocol lasted for 6 h. The patient tolerated the infusions without any hypersensitivity or anaphylactic reactions. After successful desensitization, she subsequently received the 4th and 5th cycles on an outpatient basis without any complications. At present, she has a good performance status, her disease is in partial remission, and she continues to be on follow-up.

Hypersensitivity to oxaliplatin occurs in up to 12%–15% of patients, and the incidence is likely to increase further as the drug finds more use in varied oncologic settings.[2] The exact mechanism of hypersensitivity is however not known. It is postulated to be Type I (IgE) mediated, as the most common association for developing such a reaction, is the number of treatment cycles (usually 7–10) received prior to the adverse event.[3] In the index case, however, the patient had only received one cycle before she developed a reaction to the drug. It is also prudent to question the efficacy of the chemotherapy after a patient develops a reaction, in a manner similar to asparaginase hypersensitivity. No study so far has evaluated therapeutic drug levels in patients of oxaliplatin hypersensitivity, either during or after a reaction or even after successful desensitization. It is rational to speculate that the drug molecule may be inactivated if patients develop neutralizing antibodies.

Many desensitization protocols have been in use which involve varying the infusion duration, (ranging from 3 to 15 h) and the number of steps (ranging from 5 to 13 steps).[4,5] Most protocols start with the lowest (1/10000) concentration of the total dose and gradually increase it upward (1/1000, 1/100, 1/10, and so on) as per tolerance of the patient. Standard premedications consisting of an H1 antagonist, corticosteroid, and paracetamol are used in most protocols. We used a five-step protocol as described by Gammon *et al*.[6] The total dose of oxaliplatin for our patient was 190 mg, and it was divided into five infusion bags with serially increasing concentrations (10% increments), as shown in Table 1. The most commonly used Castells.[7] protocol involves doubling the infusion rate from 2 ml/h to 80 ml/h over 12 steps in 3 h. Cortijo-Cascajares *et al*. have described a protocol involving 13 infusion steps over a period of 3.5 h.[8] These protocols, however, would require an infusion device with an accurate volume delivery system, alarms and are workforce intensive. The drug delivery is also questionable at very low infusion rates. The protocol used by Gammon *et al*., however, is easy to use, involves less number of compounding bags, and requires less workforce. However, the total duration of infusion is of moderate length. Goldberg *et al*. had used similar 5-step protocol in a series of patients, but the infusion duration ranged from 90 min to 15 h for a bag, and the final dose was administered over 11.5 h.[4] Whether the infusion duration has any association with successful desensitization is not yet known.

Another aspect to consider is the efficacy of the procedure. No studies so far have reported failure of further chemotherapy due to reactions postsuccessful desensitization. However, the number of desensitizations required for a patient may vary. In addition, some patients fail the desensitization repeatedly and are therefore not given further platinum-based chemotherapies.

Table 1: Details of the compounding bags used in our oxaliplatin desensitization protocol

Bag number	Oxaliplatin (mg)	Volume of 5% dextrose after preparation (ml)	Concentration of drug (mg/ml)	Duration of infusion (h)
1	0.019	100	0.00019	1
2	0.19	98.9	0.0019	1
3	1.9	99	0.019	1
4	19	90	0.19	1
5	171	500	0.342	2

With regard to skin testing, some authors have demonstrated high sensitivity to detect oxaliplatin hypersensitivity, whereas others have shown equivocal results. In our patient, we did not perform skin tests to confirm hypersensitivity as it is controversial till date.

To summarize, oxaliplatin desensitization protocols have made it easy to administer platinum-based chemotherapies to patients who develop reactions to it. It is safe, effective, and inexpensive. The protocol used by us is simple to administer and is tolerated well. Further studies are warranted to evaluate the mechanism of hypersensitivity which develops to oxaliplatin and whether there is the formation of any neutralizing antibodies which may hamper treatment outcome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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