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BRIEF ARTICLE

Oxaliplatin-induced severe anaphylactic reactions in metastatic colorectal cancer: Case series analysis

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Abstract

AIM: To investigate oxaliplatin-induced severe anaphylactic reactions (SAR) in metastatic colorectal cancer in a retrospective case series analysis and to conduct a systemic literature review.

METHODS: During a 6-year period from 2006 to 2011 at Kaohsiung Veterans General Hospital, a total of 412 patients exposed to oxaliplatin-related chemotherapy were retrospectively reviewed. Relevant English-language studies regarding life-threatening SAR following oxaliplatin were also reviewed in MEDLINE® and PubMed® search.

RESULTS: Eight patients (1.9%, 8 of 412 cases) were identified. Seven patients were successful resuscitated without any sequelae and one patient expired. We changed the chemotherapy regimen in five patients and rechallenged oxaliplatin use in patient 3. Twenty-three relevant English-language studies with 66 patients were reported. Patients received a median of 10 cycles of oxaliplatin (range, 2 to 29). Most common symptoms were respiratory distress (60%), fever (55%), and hypotension (54%). Three fatal events were reported (4.5%). Eleven patients (16%) of the 66 cases were rechallenged by oxaliplatin.

CONCLUSION: SAR must be considered in patients receiving oxaliplatin-related chemotherapy, especially in heavily pretreated patients. Further studies on the mechanism, predictors, preventive methods and management of oxaliplatin-related SAR are recommended.

Key words: Oxaliplatin; Anaphylactic; Colorectal cancer; Metastasis

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INTRODUCTION

Colorectal cancer (CRC) accounts for 10% to 15% of all cancers and is the third leading cause of cancer deaths in Taiwan. Oxaliplatin is a third generation platinum compound frequently used in the treatment of stage Ⅲ CRC as adjuvant chemotherapy[1] and stage Ⅳ advanced CRC[2]. Similar to other platinum compounds, oxaliplatin interacts with DNA to form intra-strand/inter-strand

DNA cross-linking that can affect DNA base pairing, replication, and gene transcription and cause cell death[3]. Among the common reasons for its withdrawal are frequent peripheral neuropathy, a delayed hypersensitivity reaction, and most troublesome, anaphylaxis when patients receive accumulated doses of oxaliplatin[4]. Hypersensitivity reaction and anaphylaxis refers to undesirable reactions produced by the normal immune system, including allergies and autoimmunity. These reactions may be damaging, uncomfortable, or occasionally fatal.

Multiple mechanisms of action have been proposed including the use of various neuroprotective agents in the hope of achieving adequate oxaliplatin doses with less neuropathy[5]. Much less is known about acute reactions such as anaphylaxis, and it is generally considered to be associated with immune-mediated effects[6,7]. The percentage of hypersensitivity reactions quoted in different studies ranges from 8% to 20%, but is usually around 10% to 12%[8]. Life-threatening severe anaphylactic reactions (SAR) have been reported but no systemic review of their incidence has been undertaken. Therefore, we performed a retrospective analysis of our patients who had been exposed to oxaliplatin and selected those who developed SAR requiring hospitalization with medical intervention. We also conducted a systemic literature review on this issue.

MATERIALS AND METHODS

Chart review

During a 6-year period from 2006 to 2011 at Kaohsiung Veterans General Hospital, a total of 412 patients exposed to oxaliplatin-related chemotherapy were retrospectively reviewed. Life-threatening SAR was defined as side effects including symptomatic bronchospasm, allergy-related edema/angioedema, hypotension or anaphylaxis (grade Ⅲ/Ⅳ anaphylactic reactions reference by NIH common Toxicity Criteria v3.0) requiring hospitalization and medical interventions[9]. The oxaliplatin-related chemotherapy regimen (FOLFOX) consisted of leucovorin 200 mg/m^2 as a 2-h infusion, and oxaliplatin 85 mg/m^2 given as a 2-h infusion in 500 mL of dextrose 5% *via* a Y-connector, followed by a 46-h infusion of 5-fluorouracil 2500 mg/m^2, repeated every 2 wk. Antiemetic prophylaxis with a 5HT3-receptor antagonist was administered. The use of implantable ports and disposable or electronic pumps allowed chemotherapy to be administered on an inpatient basis.

Data collection and literature review

Information collected included age, sex, allergy history, primary CRC site, tumor, nodes, metastasis classification, CRC stage, previous chemotherapy regimens, previous oxaliplatin-related chemotherapy cycles, oxaliplatin dosage, tumor response, onset time after oxaliplatin infusion, and outcome. Relevant English-language studies regarding life-threatening SAR following oxaliplatin were also reviewed. We searched the relevant studies by entering keywords "severe side effect after oxaliplatin", "life-threatening reaction after oxaliplatin" and "severe anaphylactic reaction after oxaliplatin" in MEDLINE® and PubMed® searches.

RESULTS

Patient characteristics

Eight patients (1.9%, 8 of 412 cases) were identified who developed life-threatening SAR, which occurred after infusion of oxaliplatin-related chemotherapy. The patients' characteristics were described in Table 1. There were 4 females and patients' age ranged from 36 to 72 years. Three patients had rectal cancer, 4 patients had sigmoid colon cancer, and 1 patient had descending colon cancer. Two patients had an allergy history to alcohol and flurbiprofen respectively. All patients had stage Ⅳ metastatic disease and received several lines of different chemotherapy regimens. Patients had received 5-29 cycles of oxaliplatin-related chemotherapy. Oxaliplatin dosages were 85 mg/m^2 in six patients and 90 mg/m^2 in one patient. Stable disease was achieved in three patients and progressive disease in five patients. Onset time after oxaliplatin infusion ranged from immediate to two hours. Seven patients were successfully resuscitated with oxygen support and medical interventions and fully recovered without any sequelae. However, one patient suffered from SAR and shock status 20 min after infusion of oxaliplatin. Despite cardiopulmonary resuscitation and use of inotropic agents, this patient expired 50 min later. We changed the chemotherapy regimen in five patients and rechallenged oxaliplatin use in patient 3. Because the patient 3's disease manifestations responded well to FOLFOX chemotherapy regimen, continuation was felt to be desirable. We have thus decided to attempt rechallenge of oxaliplatin by prolonging the infusion rate and using premedication with an additional 100 mg hydrocortisone plus diphenhydramine before the next treatment course. Fortunately, no anaphylactic reactions developed thereafter.

Literature review

Twenty-three relevant English-language studies, published from 1997-2011, regarding SAR following oxaliplatin-related chemotherapy were reported (Table 2). All studies were retrospective; few included the same patients. We found 59 reported cases that fitted the definition of life-threatening SAR from MEDLINE® and PubMed®[8-30]. Together with the 8 cases we presented, the median cycles of oxaliplatin given before SAR developed was 10 (range, 2-29). Most common symptoms were respiratory distress (60%), fever (55%), and hypotension (54%). Three fatal events were reported (4.5%). Eleven patients from these 66 cases were rechallenged with oxaliplatin.

DISCUSSION

According to previous studies, the estimated incidence of oxaliplatin-induced SAR was less than 2%[10,17,18,24,31]. In 2007, Lee *et al*[24] reported the incidence of SAR as 1.32%

Table 1 Clinical characteristics of patients with life-threatening severe anaphylactic reactions following oxaliplatin chemotherapy (n = 8)

Patient	Sex	Age (yr)	Allergy history	Primary CRC site	TNM classification	Stage	Previous chemotherapy regimens	Previous oxaliplatin chemotherapy cycles	Oxaliplatin dose (mg/m^2)	Tumor response	Presenting symptoms	Onset time	Outcome	Rechallenge
1	F	50	Alcohol	Rectum	T4N0M1	Ⅳ	FOLFIRI x12, FOLFOX x10	10	85	SD	Consciousness loss, dizziness, shock	30 min	Recovery	No
2	M	71	Nil	Rectum	T2N1M1	Ⅳ	FOLFOX x12, FOLFIRI + Bevacizumabx12, FOLFOX x1	13	85	PD	Consciousness loss, shock	20 min	Fatal	No
3	M	36	Nil	Sigmoid colon	T4N2M1	Ⅳ	FOLFIRI x13, FOLFOX + Bevacizumab x5, FOLFIRI + Cetuximab x5, FOLFOX x7	12	90	PD	Consciousness loss, respiratory distress, cold sweating	Immediate	Recovery	Yes
4	F	57	Nil	Sigmoid colon	T1N0M1	Ⅳ	FOLFIRI x5, FOLFOX x7, FOLFIRI + Bevacizumabx18, FOLFOX + Bevacizumab x1	8	85	PD	Respiratory distress, cold sweating	2 h	Recovery	No
5	F	68	Nil	Sigmoid colon	T3N2M1	Ⅳ	FOLFIRI x12, FOLFOX x8	8	85	SD	Angioedema, slurred speech, respiratory distress	30 m	Recovery	No
6	F	72	Nil	Descending colon	T4N1M1	Ⅳ	FOLFIRI x7, FOLFOX x3, FOLFIRI x12, FOLFOX x2	5	85	PD	Nausea, vomiting, shock,	10 min	Recovery	No
7	M	59	Flurbiprofen	Rectum	T3N2M1	Ⅳ	FOLFOX x19, FOLFIRI x8, FOLFOX x10	29	85	SD	Consciousness loss, respiratory distress, cold sweating	Immediate	Recovery	No
8	M	62	Nil	Sigmoid colon	T3N1M1	Ⅳ	FOLFIRI + Bevacizumabx6, FOLFOX x7	7	85	PD	Consciousness loss, respiratory distress, cold sweating	20 min	Recovery	No

M: Male; F: Female; CRC: Colorectal cancer; TNM: Tumor, nodes, metastasis; PD: Progressive disease; SD: Stable disease; FOLFIRI: Chemotherapy regimen including 5-fluorouracil, leucovorin, irinotecan; FOLFOX: Chemotherapy regimen including 5-fluorouracil, leucovorin, oxaliplatin.

Table 2 Studies on severe anaphylactic reactions following oxaliplatin, including data published from 1997 to 2012 in English (24 studies, *n* = 66)

Ref.	Published year/region	Patient No.	Age (yr)	Male/female	Previous oxaliplatin cycles	Oxaliplatin dose (mg/m^2)	Presenting symptoms	Onset time after oxaliplatin infusion	Outcome
de Gramont *et al*[10]	1997/France	5	NA	NA	NA	NA	NA	NA	Recovery
Tournigand *et al*[11]	1998/France	5	59-77	3/2	5-12	85-100	Reduced blood pressure, flushing, headache, tachycardia, respiratory distress	Immediate	Recovery
Larzillière *et al*[12]	1999/France	1	55	1/0	5	85	Flushing, profuse sweats, arterial hypertension, tachycardia	30 min	Recovery
Médioni *et al*[13]	1999/France	1	63	1/0	6	100	Visual disturbances, edema, tachycardia, severe hypotension, anaphylactic shock	Immediate	Recovery
Sørbye *et al*[14]	2000/Norway	1	40, 52	1/0	8	85	Severe thrombocytopenia	Immediate	Recovery
Santini *et al*[15]	2001/Italy	1	52	1/0	6	60	Chills, fever, nausea, vomiting, crampy abdominal pain, diarrhea, hypotension	15 min	Recovery
Schüll *et al*[16]	2001/Austria	1	54	1/0	5	85	Flush, generalised erythema of the trunk, nausea, hypotension	30 min	Recovery
Brandi *et al*[17]	2003/Italy	9	NA	NA	2-17	NA	Dyspnea, laryngospasm, agitation, tachycardia, precordial pain, erythema, sweating	NA	Recovery
Thomas *et al*[18]	2003/United States	1	50	0/1	9	NA	Fever, respiratory distress	2 h	Recovery
Lenz *et al*[19]	2003/Germany	2	NA	NA	NA	85	Severe abdominal, chest pain.	Immediate	Recovery
Bhargava *et al*[20]	2004/United States	1	50	0/1	12	NA	Palpitation, flushing, hypotensive, wheezing	15 min	Recovery
González-Mahave *et al*[21]	2005/Spain	2	43, 44	1/1	4, 11	NA	Respiratory collapse, fever	Immediate	Recovery
Maindrault-Goebel *et al*[22]	2005/France	3	NA	NA	NA	NA	Anaphylactic shock	NA	Recovery
Siu *et al*[8]	2006/Hong Kong	2	NA	NA	NA	100	Hypotension, oxygen desaturatio, full-blown anaphylactic reactions	NA	NA
Tze *et al*[23]	2006/China	1	60	0/1	12	NA	Anaphylactic shock	Immediate	Recovery
Lee *et al*[24]	2006/Taiwan	4	36-74	NA	6-7	85-100	Anaphylactic shock, hypertensive crisis	5-50 min	Recovery
Yanqi *et al*[25]	2007/China	1	52	1/0	6	150 mg	Anaphylactic shock	10 min	Recovery
Santodirocco *et al*[26]	2008/Italy	1	44	0/1	14	85	Acute thrombocytopenia, hemolysis, bleeding	1 h	Recovery
Shao *et al*[27]	2008/Taiwan	1	64	1/0	23	NA	Thrombocytopenia	1 h	Fatal
Chay *et al*[9]	2010/Singapore	11	36-75	4/7	NA	NA	Respiratory collapse, flushing, hypokalemia	NA	Recovery
Pietrantonio *et al*[28]	2010/Italy	1	NA	NA	NA	NA	Acute thrombocytopenia	NA	Recovery
Potenza *et al*[29]	2010/Italy	1	46	1/0	6	85	Respiratory collapse	10 h	Recovery
Teng *et al*[30]	2011/Taiwan	1	78	1/0	17	85	Pancytopenia, coagulopathy, intracranial hemorrhage	30 min	Fatal
Wang *et al*, this study	2012/Taiwan	7	36-72	3/4	5-29	85-90	Consciousness loss, chest tightness, cold sweating, nausea, vomiting, shock	immediately to 2 h	1 fatal

NA: Not applicable.

(4 of 303 cases) in Taiwan. In our study, the incidence is 1.9% (8 of 412 cases). Multiple suggestions to reduce the incidence of adverse reactions have been proposed, including the use of various neuroprotective agents, in the hope of achieving adequate oxaliplatin doses with less neuropathy[5]. Much less is known about acute reactions such as anaphylaxis, but this is generally considered to be associated with immune-mediated effects, as evidenced by detection of drug-dependent IgG antibodies with or without complement[6,7]. Two independent pathogenetic mechanisms have been proposed for this toxicity. Some authors described the formation of autoantibodies to erythrocytes and, more rarely, to platelets and neutrophils as a result of oxaliplatin adsorption on blood cells[32]. By contrast, other authors reported high levels of cytokines [i.e., interleukin (IL) 6, IL10 and tumor necrosis factor-α] suggesting that oxaliplatin-dependent toxicity may be triggered by a massive release of pro-inflammatory molecules[33].

In literature reviews, SAR developed after several cycles of oxaliplatin chemotherapy (median cycles before SAR is 10), suggesting a sensitization process of type I hypersensitivity due to the rapid appearance of symptoms[22,34]. Based on Chay *et al*[9], females appeared more prone to severe oxaliplatin reactions for which the reason remains unclear, and all females manifested acute hypokalemia. Recently reported ex-vivo work suggests that oxaliplatin may interfere with voltage-gated potassium channels[35] and hypothesizes that axonal membrane hyperpolarization[36,37] may account for the observed hypokalemia, with potassium ion channel activation resulting in an intracellular influx of potassium. However, in our study there were no such findings including female predominance and hypokalemia after the episode.

Theoretically, prolongation of the infusion rate with premedication including steroids and antihistamines could be a method to prevent SAR after oxaliplatin use. We adopted this strategy before rechallenging oxaliplatin in patient 3. However, in 2001 Stahl *et al*[38] reported that allergic reactions to oxaliplatin may still occur after steroid prophylaxis. In 2006, Siu *et al*[8] reported premedications with steroid and chlorpheniramine seemed ineffective in preventing SAR. In 2011, Siu *et al*[39] developed a simple rechallenge protocol for mild hypersensitivity reactions, including intravenous dexamethasone, diphenhydramine and ranitidine, as well as prolongation of the oxaliplatin infusion time with a high success rate of 70%. Why did the anaphylactic reactions disappear after rechallenge of oxaliplatin in patient 3? A possible explanation for the disappearance of symptoms may be the much lower peak plasma concentrations of the platinum compound and its metabolites in case of a protracted infusion[3], thus resulting in a minor and/or delayed, clinically negligible cytokine release reaction. In literature reviews, five of eleven rechallenged patients could tolerate oxaliplatin with no or minimal discomfort. However, there were still three patients developing SAR after receiving prolonged infusion of oxaliplatin. There were also reported cases initially having only a mild hypersensitivity reaction to oxaliplatin, who developed SAR after rechallenge with prolonged infusion schedule[22]. Therefore, it seems that prolonged infusion of oxaliplatin or using a desensitization program could only benefit a few patients who developed SAR. So, changing the chemotherapy regimen might be a better choice.

The mortality rate of oxaliplatin-related SAR was 4.5% (3 of 66 patients). In 2008, Shao *et al*[27] reported a fatal thrombocytopenia with a large intracranial hemorrhage with brain herniation after oxaliplatin chemotherapy. In 2011, Teng *et al*[30] reported another fatal pancytopenia with intracranial hemorrhage after oxaliplatin treatment. In our study, the patient who died initially presented with anaphylactic shock and loss of consciousness immediately after oxaliplatin infusion. All these three patients had been heavily pretreated with oxaliplatin and had received 23, 17 and 13 cycles of oxaliplatin treatment, respectively. To counteract the underlying immune-mediated mechanism, the use of steroids seems to be one of the most cost-effective approaches, especially when the patient's condition is life threatening[7,40]. This may also explain the fatalities in the patients reported by Shao *et al*[27], Teng *et al*[30] and our patient, who did not receive a steroid. Are there any predictors or risk factors for this rare but life-threatening event before oxaliplatin use? In 2011, Seki *et al*[41] reported a higher neutrophil count and lower monocyte count were two risk factors for grade 3/4 reactions in oxaliplatin-induced hypersensitivity reactions in Japanese patients. However, we didn't observe such a relationship in our study and the literature review.

Target therapy with monoclonal antibodies, including bevacizumab, cetuximab, and panitumumab, can also result in SAR[42]. Up till April 2012, there have been 14 698 people reported to have side effects when taking bevacizumab. Among them, 87 people (0.59%) have SAR[43]. In our study, one patient (patient 4) developed SAR after bevacizumab and oxaliplatin infusion. In our hospital, bevacizumab was started first and infused over 1-h. Oxaliplatin was infused after bevacizumab infusion. This patient developed SAR about 3 h after bevacizumab infusion and 2 h after oxaliplatin infusion. It is very difficult to differentiate the cause of SAR in this patient. But due to the time of onset of SAR, it is reasonable to suspect oxaliplatin.

Our study does have several limitations. First, being a retrospective review, it is difficult to confirm now whether those observed reactions are genuine hypersensitivity reactions or whether they developed 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.

In conclusion, SAR is rare but serious, and must be considered in patients receiving oxaliplatin-related che-

motherapy, especially in heavily pretreated patients. Physicians should be cautious when patients have repeated symptoms or signs of allergic reaction to oxaliplatin. At the moment, the mechanisms underlying oxaliplatin-related SAR remain uncertain. Prevention with prolongation of the infusion rate, steroid use and antihistamines are still in debate. Rechallenge with oxaliplatin is suggested only in carefully selected patients and should be used with caution. We recommend changing the chemotherapy regimen in patients experiencing oxaliplatin-induced SAR. Further extensive examinations with a large number of patients to determine the mechanism, the predictors, preventive methods and management strategy of oxaliplatin-induced SAR are recommended.

COMMENTS

Background

Oxaliplatin is a third generation platinum compound frequently used in the treatment of stage Ⅲ and stage Ⅳ colorectal cancer. Among the side effects of this agent, hypersensitivity reaction and anaphylaxis refers to undesirable reactions produced by the normal immune system, including allergies and autoimmunity. These reactions may be damaging, uncomfortable, or occasionally fatal. The percentage of hypersensitivity reactions quoted in different studies ranges from 8% to 20%. The authors presented their experience in this retrospective study and conducted a systemic review.

Research frontiers

Much less is known about acute reactions such as anaphylaxis, but it is generally considered to be associated with immune-mediated effects, as evidenced by detection of drug-dependent IgG antibodies with or without complement. Further extensive examination with a large number of patients to determine the mechanism, the predictors, preventive methods and management strategy of oxaliplatin-induced severe anaphylactic reactions (SAR) are recommended.

Innovations and breakthroughs

Life-threatening SAR have been reported but no systemic review had been performed. Here, the authors performed a retrospective analysis of the patients who had been exposed to oxaliplatin and selected those who developed SAR requiring hospitalization with medical intervention and conducted a systemic literature review on this issue.

Applications

Physicians should be cautious when patients have repeated symptoms or signs of allergic reaction to oxaliplatin. The effectiveness of prevention with prolongation of the infusion rate, steroid use and antihistamines is still in debate. Rechallenge of oxaliplatin is suggested only in highly selected patients and should be used with caution. The authors recommend changing the chemotherapy regimen in patients experiencing oxaliplatin-induced SAR.

Peer review

This manuscript is a retrospective analysis of oxaliplatin chemotherapy-induced SAR at Kaohsiung Veterans General Hospital in Taiwan. In addition, the authors have conducted a literature review on the same issue. This side effect is rare but is a life-threatening event; the authors have made some recommendations on the use of oxaliplatin as chemotherapy. This is important information which needs to be reported.

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