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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 systematic 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[9]. 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[40]. 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[41]. Much less is known about acute reactions such as anaphylaxis, and it is generally considered to be associated with immune-mediated effects[41,42,43]. 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/m² as a 2-h infusion, and oxaliplatin 85 mg/m² 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/m², repeated every 2 wk. Antimetic 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 chemotherapeutic 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/m² in six patients and 90 mg/m² 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’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%[10,17,14,24,31]. 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 | Previous chemotherapy regimens | Previous oxaliplatin chemotherapy cycles (mg/m²) | Oxaliplatin dose (mg/m²) | 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 + Bevacizumab x12, 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 + Bevacizumab x38, 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 | Consciousness loss, respiratory distress, cold sweating | 30 m | Recovery | No |
| 6 | F | 72 | Nil | Descending colon | T4N1M1 | IV | FOLFIRI x7, FOLFOX x3, FOLFIRI + Bevacizumab 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 + Bevacizumab x6, 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                              | Reduced blood pressure, flushing, headache, tachycardia, respiratory distress        | NA                                  | Recovery |
| Tournigand et al\[^{11}\] | 1998/France | 5           | 59-77    | 3/2         | 5-12                        | 85-100                          | NA                                                                                | NA                                  | Recovery |
| Lazzi\[^{er}^\] Li 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                              | Chills, fever, nausea, vomiting, crampy abdominal pain, diarrhea, hypotension      | Immediate                           | Recovery |
| Larzillière et al\[^{15}\] | 2001/Italy  | 1           | 54       | 1/0         | 5                           | 85                              | Flush, generalised erythema of the trunk, nausea, hypotension                    | 30 min                              | Recovery |
| Sørbye et al\[^{16}\] | 2000/Norway | 1           | 60       | 0/1         | 8                           | 100                             | Severe thrombocytopenia                                                        | Immediate                           | Recovery |
| Santini et al\[^{17}\] | 2001/Italy  | 1           | 52       | 1/0         | 6                           | 60                              | Visual disturbances, edema, tachycardia, severe hypotension, anaphylactic shock    | Immediate                           | Recovery |
| Brandi et al\[^{18}\] | 2003/Italy  | 9           | NA       | NA          | 2-17                        | NA                              | Dyspnea, laryngospasm, agitation, tachycardia, precardial pain, erythema, sweating | NA                                  | Recovery |
| Thomas et al\[^{19}\] | 2003/United States | 1         | 50       | 0/1         | 9                           | NA                              | Fever, respiratory distress                                                      | 2 h                                 | Recovery |
| Lenz et al\[^{20}\] | 2003/Germany | 2           | NA       | NA          | NA                          | 85                              | Severe abdominal, chest pain.                                                    | Immediate                           | Recovery |
| Bhargava et al\[^{21}\] | 2004/United States | 1         | 50       | 0/1         | 12                          | NA                              | Palpitation, flushing, hypotensive, wheezing                                      | 15 min                              | Recovery |
| González-Mahave et al\[^{22}\] | 2005/Spain  | 2           | 43, 44   | 1/1         | 4, 11                       | NA                              | Respiratory collapse, fever                                                      | Immediate                           | Recovery |
| Maindrault-Goebel et al\[^{23}\] | 2005/France | 3           | NA       | NA          | NA                          | 100                             | Anaphylactic shock                                                               | NA                                  | Recovery |
| Siu et al\[^{24}\] | 2006/Hong Kong | 2           | NA       | NA          | NA                          | 100                             | Hypotension, oxygen desaturation, full-blown anaphylactic reactions               | NA                                  | NA       |
| Tze et al\[^{25}\] | 2006/China  | 1           | 60       | 0/1         | 12                          | NA                              | Anaphylactic shock                                                               | Immediate                           | Recovery |
| Lee et al\[^{26}\] | 2006/Taiwan | 4           | 36-74    | NA          | 6-7                         | 85-100                          | Anaphylactic shock, hypertensive crisis                                           | 5-50 min                            | Recovery |
| Yang et al\[^{27}\] | 2007/China  | 1           | 52       | 1/0         | 6                           | 150 mg                          | Acute thrombocytopenia, hemolysis, bleeding                                        | 1 h                                 | Recovery |
| Santostiocco et al\[^{28}\] | 2008/Italy  | 1           | 44       | 0/1         | 14                          | 85                              | Anaphylactic shock                                                               | 1 h                                 | Recovery |
| Shao et al\[^{29}\] | 2008/Taiwan | 1           | 64       | 1/0         | 23                          | NA                              | Respiratory collapse, flushing, hypokalemia                                       | 1 h                                 | Fatal    |
| Chay et al\[^{30}\] | 2010/Singapore | 11         | 36-75    | 4/7          | NA                          | 100                             | Anaphylactic shock                                                               | Immediate                           | Recovery |
| Pietrantonio et al\[^{31}\] | 2010/Italy  | 1           | NA       | NA          | NA                          | NA                              | Acute thrombocytopenia                                                           | NA                                  | Recovery |
| Potenza et al\[^{32}\] | 2010/Italy  | 1           | 46       | 1/0         | 6                           | 85                              | Respiratory collapse                                                            | 10 h                                | Recovery |
| Teng et al\[^{33}\] | 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.
of oxaliplatin. There were also reported cases initially patients developing SAR after receiving prolonged infusion minimal discomfort. However, there were still three pa-
kine release reaction. In literature reviews, five of eleven ing in a minor and/or delayed, clinically negligible cyto-
metabolites in case of a protracted infusion plasma concentrations of the platinum compound and its disappearance of symptoms may be the much lower peak 
domiance and hypokalemia after the episode.

perpolarization oxaliplatin may interfere with voltage-gated potassium 
remains unclear, and all females manifested acute hypo-
ected by a massive release of pro-inflammatory mole-
ules\[31\].

In literat\[22,34\]ure 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 symp-
toms\[32,46\]. Based on Chay et al\[6\], females appeared more prone to severe oxaliplatin reactions for which the reason remains unclear, and all females manifested acute hypo-
klema. Recently reported ex-vivo work suggests that oxaliplatin may interfere with voltage-gated potassium 
channels\[33\] and hypothesizes that axonal membrane hy-
perpolarization\[36,37\] may account for the observed hypo-
klema, with potassium ion channel activation resulting in 
in an intracellular influx of potassium. However, in our 
study there were no such findings including female pre-
dominance 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\[30\] reported that al-
lergic reactions to oxaliplatin may still occur after steroid prophylaxis. In 2006, Siu et al\[30\] reported premedications 
with steroid and chlorpheniramine seemed ineffective in 
preventing SAR. In 2011, Siu et al\[30\] 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\[8\], thus result-
ing in a minor and/or delayed, clinically negligible cyto-
kine release reaction. In literature reviews, five of eleven rechallenged patients could tolerate oxaliplatin with no 
or minimal discomfort. However, there were still three pa-
tients 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\[21\]. 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 under-
lying 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 threaten-
ing\[7,40\]. 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 14698 
people reported to have side effects when taking beva-
cizumab. 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. Ox-
aliplatin was infused after bevacizumab infusion. This 
patient developed SAR about 3 h after bevacizumab infu-
sion 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, be-
ing a retrospective review, it is difficult to confirm now 
whether those observed reactions are genuine hypersen-
sitivity reactions or whether they developed as a result 
of oxaliplatin infusion only, although the temporal relation-
ship between infusion and onset of reaction is suggestive. 
Therefore, it is possible that the risk may have been over-
estimated. We can also argue the other way round, that is, 
some mild reactions may have been missed resulting in 
derestimation.

In conclusion, SAR is rare but serious, and must be 
considered in patients receiving oxaliplatin-related che-
Wang JH et al. Oxaliplatin-induced severe anaphylactic reactions

mothers, 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 gener-
ally 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.

REFERENCES

1 André T, Boni C, Mournedj-Boudiaf L, Navarro M, Taberner J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridge-water J, Tabah-Fisch I, de Gramont A. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004; 350: 2343-2351

2 Giacchetti S, Perpont B, Zidani R, Le Bail N, Faggiuolo R, Focan C, Chollet P, Llorý JF, Letourneur Y, Coudert B, Bertheaut-Cvitkovic F, Larregain-Fournier D, Le Rol A, Walter S, Adam R, Misset JL, Lévi F. Phase III multicenter randomized trial of oxaliplatin added to chromomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 2000; 18: 136-147

3 Culy CR, Clemett D, Wiseman LR. Oxaliplatin. A review of its pharmacological properties and clinical efficacy in metastatic colorectal cancer and its potential in other malignancies. Drugs 2000; 60: 895-924

4 Saif MW. Hypersensitivity reactions associated with oxaliplatin. Expert Opin Drug Saf 2006; 5: 687-694

5 Grotthey A, Hart LL, Rowland KM, Ansari RH, Alberts SR, Chowhan NM, Shlipsky A, Hochster HS. Intermittent oxaliplatin administration and time-to-treatment failure in metastatic colorectal cancer: Final results of the phase III CONCePT trial. J Clin Oncol 2008; 26 (Suppl): Abstract 4010 Available from: URL: http://www.asco.org/ascov2/Meetings/Abstracts&vmview=abst_detail_view&confID=55&abstractID=34113

6 James E, Podoltsv N, Salahi E, Curtis BR, Saif MW. Oxaliplatin-induced immune thrombocytopenia: another cumulative dose-dependent side effect? Clin Colorectal Cancer 2009; 8: 220-224

7 Bautista MA, Stevens WT, Chen CS, Curtis BR, Aster RH, Hsueh CT. Hypersensitivity reaction and acute immune-mediated thrombocytopenia from oxaliplatin: two case reports and a review of the literature. J Hematol Oncol 2010; 3: 12

8 Siu SW, Chan RT, Au GK. Hypersensitivity reactions to oxaliplatin: experience in a single institute. Ann Oncol 2006; 17: 259-261

9 Chay WY, Chew L, Yeoh TT, Tan MH. An association between transient hypokalemia and severe acute oxaliplatin-related toxicity predominantly in women. Acta Oncol 2010; 49: 515-517

10 de Gramont A, Vignoud J, Tournigand C, Louvet C, André T, Varette C, Raymond E, Moreau S, Le Bail N, Kruilik M. Oxaliplatin with high-dose leucovorin and 5-fluorouracil 48-hour continuous infusion in pretreated metastatic colorectal cancer. Eur J Cancer 1997; 33: 214-219

11 Tournigand C, Maindrault-Goebel F, Louvet C, de Gramont A, Kruilik M. Severe anaphylactic reactions to oxaliplatin. Eur J Cancer 1998; 34: 1297-1298

12 Larzilliére I, Brandissou S, Breton P, Lingoungou A, Gargot D, Ramain JP, Harnois C. Anaphylactic reaction to oxaliplatin: a case report. Am J Gastroenterol 1999; 94: 3387-3388

13 Médioni J, Coulon MA, Morere JF, Hennebelle F, Piperno-Neumann S, Breau JL. Anaphylaxis after oxaliplatin. Ann Oncol 1999; 10: 610

14 Surbye H, Bruserud Y, Dahl O. Oxaliplatin-induced haematological emergency with an immediate severe thrombocytopenia and haemolysis. Acta Oncol 2001; 40: 882-883

15 Santini D, Tonini G, Salerno A, Vincenzi B, Patti G, Battistoni F, Dicuonzo G, Labianca R. Idiosyncratic reaction after oxaliplatin infusion. Ann Oncol 2001; 12: 132-133

16 Schühl B, Kornek GV, Scheithauer W. Idiosyncratic reaction after oxaliplatin: circumvention by use of a continuous infusion administration schedule. Ann Oncol 2001; 12: 1653-1654

17 Brandi G, Pantaleo MA, Galli C, Falcone A, Antonuzzo A, Mordenti P, Di Marco MC, Biasco G. Hypersensitivity reactions related to oxaliplatin (OHP). Br J Cancer 2003; 89: 477-481

18 Thomas RR, Quinn MG, Schuler B, Greml J. Hypersensitiv-
ity and idiosyncratic reactions to oxaliplatin. Cancer 2003; 97: 2501-2507

19 Lenz G, Hacker UT, Kern W, Schalhorn A, Hiddemann W. Adverse reactions to oxaliplatin: a retrospective study of 25 patients treated in one institution. Anticancer Drugs 2003; 14: 731-733

20 Bhargava P, Gammon D, McCormick MJ. Hypersensitivity and idiosyncratic reactions to oxaliplatin. Cancer 2004; 100: 211-212
Wang JH et al. Oxaliplatin-induced severe anaphylactic reactions

21 González-Mahave I, Lobera labairu T, Blasco Sarramián A, del Pozo Gil MD, Zorrilla M, Vélez de Mendizábal E. Anaphylaxis produced by oxaliplatin. J Investig Allergol Clin Immunol 2005; 15: 75-77

22 Maindralt-Goebel F, André T, Tournigand C, Louvet C, Perez-Staub N, Zeghlith N, De Gramont A. Allergic-type reactions to oxaliplatin: retrospective analysis of 42 patients. Eur J Cancer 2005; 41: 2262-2267

23 Tze CNV. Anaphylactic shock to oxaliplatin in the adjuvant context. J Pharm Technol 2006; 12: 221-225

24 Lee MY, Yang MH, Liu JH, Yen CC, Lin PC, Teng HW, Wang WS, Chou Tj, Chen PM. Severe anaphylactic reactions in patients receiving oxaliplatin therapy: a rare but potentially fatal complication. Support Care Cancer 2007; 15: 89-93

25 Yanqi C. Anaphylactic shock attributed to oxaliplatin use. Adverse Drug React J 2007; 9: 287

26 Santodirocco M, Lombardi V, Pesce C, Palumbo G, Calapbo S, Landriscina M. Life-threatening oxaliplatin-induced acute thrombocytopenia, hemolysis and bleeding: a case report. Acta Oncol 2008; 47: 1602-1604

27 Shao YY, Hong RL. Fatal thrombocytopenia after oxaliplatin-based chemotherapy. Anticancer Res 2008; 28: 3115-3117

28 Pietrantonio F, Di Bartolomeo M, Buzzoni R, Bajetta E. Acute immune-mediated thrombocytopenia due to oxaliplatin administration: a case report. Tumori 2010; 96: 154-156

29 Potenza S, Nasti G, Ottaviano A, Filippelli A, Rossi F, Capuano A. Severe respiratory symptoms to oxaliplatin infusion: a case report of delayed hypersensitivity reaction. Invest New Drugs 2010; 28: 185-186

30 Teng CJ, Hsieh YY, Chen KW, Chao TC, Tzeng CH, Wang WS. Sudden-onset pancytopenia with intracranial hemorrhage after oxaliplatin treatment: a case report and literature review. Jpn J Clin Oncol 2011; 41: 125-129

31 Misset JL. Oxaliplatin in practice. Br J Cancer 1998; 77 Suppl 4: 4-7

32 Curtis BR, Kaliszewski J, Marques MB, Saif MW, Nabelle L, Blank J, McFarland JG, Aster RH. Immune-mediated thrombocytopenia resulting from sensitivity to oxaliplatin. Am J Hematol 2006; 81: 193-198

33 Koutras AK, Makatsoris T, Paliogianni F, Kopsida G, Onyeadum A, Gogos CA, Mouzaki A, Kalofonos HP. Oxaliplatin-induced acute-onset thrombocytopenia, hemolysis and hemolysis. Oncology 2004; 67: 179-182

34 Watts SW. 5-HT in systemic hypertension: foe, friend or fantasy? Clin Sci (Lond) 2005; 108: 399-412

35 Kagiava A, Tsingotjidou A, Emmanouilides C, Theophilidis G. The effects of oxaliplatin, an anticancer drug, on potassium channels of the peripheral myelinated nerve fibres of the adult rat. Neurotoxicology 2008; 29: 1100-1106

36 Tan MH, Chay WY, Ng JH, Teh BT, Chew L. Transient bilateral abducens neuropathy with post-tetanic facilitation and acute hypokalemia associated with oxaliplatin: a case report. J Med Case Rep 2010; 4: 36

37 Kuwabara S, Kanai K, Sung JY, Oogawara K, Hattori T, Burke D, Bostock H. Axonal hyperpolarization associated with acute hypokalemia: multiple excitability measurements as indicators of the membrane potential of human axons. Muscle Nerve 2011; 43: 283-287

38 Stahl M, Köster W, Wilke H. Reaction after oxaliplatin--prevention with corticosteroids? Ann Oncol 2003; 12: 874

39 Siu SW, Chan WL, Liu KY, Choy TS, Leung TW, Au KH. Re-challenging patients with oxaliplatin allergy: the successful use of a standardised pre-medication protocol in a single institute. Clin Oncol (R Coll Radiol) 2011; 23: 558-559

40 Fontão-Wendel R, Hof P, Lazar A, Freitas D, Novis Y, Patah P, Tsujita M, Balthazar A, Pierroti M, Wendel S. Immune-mediated pancytopenia induced by oxaliplatin: a case report. Transfusion 2010; 50: 1453-1459

41 Seki K, Senzaki K, Tsukuba Y, Irooi T, Fujii M, Yamauchi H, Shiraiishi Y, Nakata I, Nishiguchi K, Matsubayashi T, Takakubo Y, Okamura N, Yamamori M, Tamura T, Sakada T. Risk factors for oxaliplatin-induced hypersensitivity reactions in Japanese patients with advanced colorectal cancer. Int J Med Sci 2011; 8: 210-215

42 Schwartzberg LS, Stephenski EJ, Fortner BV, Houts AC. Retrospective chart review of severe infusion reactions with rituximab, cetuximab, and bevacizumab in community oncology practices: assessment of clinical consequences. Support Care Cancer 2008; 16: 393-398

43 http://www.ehealthme.com/ds/avastin/anaphylactic shock.