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Oxaliplatin associated with acute kindey injury with CAPEOX regimen in a Chinese patient: A Case Report and Literature Review.

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ABSTRACT

Oxaliplatin is a third-generation platinum derivative widely used together with other chemotherapy agents known as FOLFOX or CAPEOX,also known as XELOX, to treat metastatic colorectal cancer. We described a rare case of a 53-year-old Chinese woman with metastatic colonic adenocarcinoma who received a CAPEOX regimen. After oxaliplatin infusion, hemolytic anemia, thrombocytopenia and acute kidney injury occurred. She was successfully treated, including discontinuation of oxaliplatin, continuous renal replacement therapy and steroid replacement. Oxaliplatin associated with acute kindeyinjury is a rare but life-threatening adverse drug reaction which has not been described in the specification of oxaliplatin.This is the first description of aserious side effect of oxaliplatin-induced acute kindey injury which occur faster than ever before. After a literature review, we are the first to discover that this adverse reaction seems to occur faster with CAPEOX than with FOLFOX and more men suffer from oxaliplatin-induced acute kindey injury than do women. Careful monitoring of renal function is important whenpatients with metastatic colorectal cancer receive oxaliplatin-based chemotherapy, especially CAPEOX regimen.

Keywords: oxaliplatin, acute kindey injury, CAPEOX regimen, FOLFOX regimen

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INTRODUCTION

Oxaliplatin is widely used in combination with 5-fluorouracil and folinic acid (FOLFOX) or capecitabine (CAPEOX or XELOX) as a first-line treatment for metastatic colorectal cancer.[1-3] The combination of oxaliplatin with 5-fluorouracil or capecitabine significantly improves the response rate and progression-free survival[3]. Common side effects of oxaliplatin are sensory neuropathy, neutropenia, nausea, diarrhea and thrombo cytopenia,[4-6]severe adverse drug reaction (ADR) of oxaliplatin-induced acute kindey injury (AKI) was rarely observed during its short-term administration.[5] In this report, we describe a rare case of overt oxaliplatin-induced AKI in a 53-year-old Chinese woman with metastatic colonic adenocarcinoma who received only3 cycles of CAPEOX regimen.

Case report

A 53-year-old Chinese woman initially presented with stage II metastatic colonic adenocarcinoma in 2017, and multiple biopsies showed metastases in four perivisceral lymph nodes, the results of liver ultrasonography and a chest computed tomography(CT)scan were negative. After undergoing radical surgery in April 2017, she was treated with an adjuvant CAPEOX chemotherapy regimen (using a standard oxaliplatin dose of 130 mg/m^{2}on day 1, q21d and standard doses of capecitabine with a 1000 mg/m^2 bolus on days 1-14, q21d), and she tolerated her first 2 cycles very well.

Before her third cycle of chemotherapy, laboratory tests showed that her hematological and renal functions remained normal (**Table 1**). During the infusion of oxaliplatin as part of thethird CAPEOX cycle in the outpatient department of The Affiliated YanchengHospital of Southeast University Medical College, she developed rapid onset of nausea, emesis, back pain, and one episode of pink-colored urine followed by oliguria，then sent to the intensive care unit(ICU)immediately. She exhibited an acutely decreased platelet count (from 143*10^9/L before chemotherapy on the day of treatmentto 32*10^9/L), hyperpyrexia, hypotension at 95/57 mmHg and a lactate dehydrogenase (LDH) level of 987 U/l (normal value <450). Urinalysis showed large blood, 2t protein, and 18 red blood cells and was negative for leukocyte esterase and nitrite. Although on the first day she was admitted to ICU accompanied by fever, an evaluation of normal leukocyte countand no feverday after admission for infectious diseases was negative, specifically, no Salmonella or Shigella was isolated, and no Shiga toxin was detected. A test for heparin-induced thrombocytopenia was also demonstrated negative. Further investigation revealed decreased antithrombinIII activity(AT-IIIC) at 63.4% (normal, 75-125%), a positive direct antiglobulin test (DAT) for immunoglobulin G, an increased level of blood urea nitrogen (BUN) at 18.7mmol/L (normal 1.5-8.2mmol/L), and a serum creatinine level of 363 μmol/L (normal 30-106μmol/L).There were 2 to 3schistocytes per high-power field in a peripheral blood smear; however, a renal biopsy was not performed because of the great risks of bleeding and the fear and discomfort of this old patient. All of these data supportsevere hypersensitivity reactions associated with oxaliplatin.

Table 1: The patient's laboratory tests over the course of her hospitalization (days 1–19)

	Before 3th, OxaliplatinInfusion	20 July, Day 1	17 June, Day 2	19 June, Day 3	22 June, Day 5	25 June, Day8	29 June, DischargeDay
WBC (109/L)	4.12	9.18	8.59	8.21	6.48	6.98	7.98
Platelets (109/L)	143	61	32	34	75	172	169
D-dimer（mg/L）	0.72	6.42	9.11	12.2	2.17	1.03	0.64
LDH (U/L)	174.5	987	1135	2150	342	267.8	178.5
ALT(U/L）	37.1	54.6	45.2	62	ND	35.9	28.7
Creatinine (umol/L)	40	42.4	363	359.5	253.3	116.6	76.8
BUN (mg/dL)	4.33	2.61	18.67	17.99	8.63	9.08	3.54
AT-IIIC(%)	84.94	ND	63.38	67.21	78.93	92.22	ND
Hemoglobin（g/L）	109	102	89	92.7	106	118	116

Abbreviations: WBC:white blood cell; LDH:lactate dehydrogenase; ALT: .alanine transaminase; BUN: blood urea nitrogen;AT-IIIC :antithrombinIII activity; ND:not done.

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With continuous renal replacement therapy (CRRT) for AKI and a tapering of oral methylprednisolone to suppress autoimmune reaction, 8 days after the discontinuation of oxaliplatin her condition was improved. She was hemo dynamically stable and clinically well without fever or bleeding and was transferred to the oncology department on hospital day 8. Her BUN, LDH and D-dimer were corrected at the time of discharge. A clinical follow-up examination in September 2017 was negative for signs of relapsed hemolysis or AKI.

DISCUSSION

This patient's clinical picture, with fever, markedly increased LDH level, decreased AT-IIIC levels, immune hemolytic anemia, thrombocytopenia and AKI, resembled a group of disease state stermed "drug hypersensitivity", interestingly, renal failure dominates the clinical picture of this patient.

Potential factors that might have contributed to the significant change in the patient's kindey function included acute tumor lysis syndrome(ATLS), infection and drug-related kindey injury. For this patient, although high level of uric acid (UA) is the most important basis and necessary premise of ATLS diagnosis,[**7]** the data given in the table 1 showed that the laboratory test of UA was normal, the results of WBC wasnot abnormal and germiculture wasalso negative implied that infection did not occur and cause kindey injury in the patient. The other possible contributing factor to the kindey injury was chemotherapy drug.

Because of the acute onset of her symptoms shortly after infusion was initiated, her AKI was most likely induced by her chemotherapy agents, particularly oxaliplatin. Althoughspecification of neither oxaliplatin nor capecitabine mentions AKI-related ADR, there have been multiple reports of different forms of renal injury related to oxaliplatin in combination with other agents, such as in FOLFOX or CAPEOX regimens in recent years,[8-21]furthermore the patient's Naranjo ADR probability scale of 6 revealed that his AKI was probably precipitated by oxaliplatin. The Naranjonomogram is a 10-pointquestionnaire for determining the likelihood of whether an ADR is actually due to the drug, rather than the result of otherfactors, in which terms such as definite (≥9 points), probably (5–8points), possible (1–4 points), and doubtful (0 points) are calculated.[22]

On the basis of literature review, Oxaliplatin-induced AKI appears to occur after multiple cycles of the drug. It is interesting to note that different regimens of oxaliplatin led to AKI variances, as shown in Table 2. Oxaliplatin-related AKI occurs mostly after the 6th course of FOLFOX; in contrast, this reaction usually develops within the 4thoxaliplatin infusion in CAPEOX regimen. Compared with the CAPEOX regimen which includes capecitabine and oxaliplatin, only calcium folinate is added to the FOLFOX regimen which also includes fluorouracil and oxaliplatin, because capecitabine, inside the body, is metabolised to fluorouracil through which it acts and therefore, folinatemay play a critical role in postponing or avoidingthis adverse reaction.

Table2: Characteristics of Patients Who Developed oxaliplatin-Induced Acute Kindey Injury

Study	Year	Age	Sex	Tumor Type	Therapy regimen	Cycle ofOxaliplatin	Symptoms	LaboratoryFindings	DAT	Renal Biopsy	follow-up Recovery
Desrameet al,(8)	1999	66	F	M colon cancer	FOLFOX	45th	Back pain, fever, chills,jaundice, dark urine	Anemia, AKI, spherocytosis, increased bilirubin and LDH	IgG/C3d	ND	YES
Pinottiet al, (9)	2002	57	M	M olon cancer	FOLFOX	17th	Abdominal pain, fever, oliguria	Increased Cr	ND	ND	YES
Hofheinzet al, (10)	2004	60	M	M colon cancer	FOLFOX	6th	Back pain, jaundice, dark urine	Anemia, thrombocytopenia, increased bilirubin, LDH and Cr	IgG/C3d	ND	YES

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Dahabrehet al, (11)	2006	52	M	Colon cancer	FOLFOX	4th	Hematuria, anuria	Thrombocytopenia, increased bilirubin,LDH, and Cr	—	ND	YES
Butiet al, (12)	2007	64	M	M colon cancer	FOLFOX	11th	Back pain, chill, sclera,jaundice and dark urine	Anemia, hrombocytopenia, increased bilirubin, LDH, Cr, hemoglobinuria,albuminuria	IgG	ND	YES
Coboet al, (13)	2007	59	F	M colon cancer	FOLFOX	15th	Back pain, dark urine,oliguria, hematemesis	Anemia, thrombocytopenia, increased LDH, Cr	IgG/ C3d	ND	YES
Phanet al, (14)	2009	65	M	M colon cancer	FOLFOX	5th	Back pain, oliguria, dark urine	Thrombocytopenia, increased bilirubin,LDH, Cr	—	ND	YES
Márquezetal, (15)	2013	66	M	M colon cancer	FOLFOX	15th	Asymptomatic pancytopenia	Thrombocytopenia,Anemia, increased Cr	NA	NA	YES
Ali Y Jet al, (16)	2014	40	F	M colon cancer	mFOLFOX7	36th	Abdominal pain,low-grade fever,oliguria	Severe anemia, thrombocytopenia, increased Cr, IB, and LDH	—	+	YES
P Phullet al, (17)	2016	57	M	M colon cancer	FOLFOX	18th	Black-colored urine,	increased Cr, bilirubin	IgG/ C3d	ND	YES
Ulusakaryaet al, (18)	2010	47	M	M colon cancer	FOLFOX	12th	Abdominal pain, chills, fever, dark urine	Increased Cr, LDH, hematuria,hemoglobinuria	+	ND	YES
Niuet al, (19)	2012	68	F	M colon cancer	FOLFOX	2th	Sudden-onset chest pain,fever and high blood pressure and heart rate during oxaliplatin infusion. confusion, jaundice	Thrombocytopenia, increased Cr, bilirubin, LDH, ADAMTS13 deficiency	IgG/ C3d	ND	YES

L Meng et al, (20)	2015	76	F	M colon cancer	FOLFOX	6th	Nausea, bloody emesis, abdominal pain,pink-colored urine	Anemia, AKI, spherocytosis, increased bilirubin, and LDH	IgG/ C3d	—	YES
Ito et al, (21)	2012	54	F	Colon cancer	Various regimens including FOLFOX, XELOX	34th(XELOX 4th)	Malaise, dizziness, nausea,anorexia	Severe anemia, hrombocytopenia, increased Cr, LDH	IgG/ C3d	ND	YES
HjJiet al, (a)	2018	53	F	M colon cancer	XELOX	3th	Abdominal pain,fever, oliguria	Anemia, AKI and increased LDH, Cr	IgG	ND	YES

a: Our patient; acute renal failure: AKI; Cr: creatinine; LDH: lactate dehydrogenase; IB: indirect bilirubin; ND: not done

Although the exact mechanism of action for the special phenomenonis not clear, it is believed to be related to the oxaliplatin accumulates in RBCs(red blood cells) after repeated administration[23] or folinate could promote the formation of red blood cells and mature erythrocytes[24],this possibility remains to be explored in the future.

Table 2 also shows men appear more prone to oxaliplatin-induced AKI, and this finding most likely reflects the predominance of colorectal cancer in males, as well as the number of oxaliplatin-induced AKI patient administrated FOLFOX regimenis more than that of patient with CAPEOX regimen, because patients with metastatic colorectal cancer received FOLFOX regimenas prime regimen in the past for a long time.[25]

CONCLUSION

This is the first description of a serious side effect of oxaliplatin-induced AKI which occur faster than ever before. For patients received CAPEOX regimen, careful monitoring of renal function, as well as changes in hematological parameters, is important, because oxaliplatin-induced AKI fast and suddenly.

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