Case Report

A Severe Oxaliplatin-induced Hypersensitivity Reaction

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Abstract: We describe the case of a 74-year-old man who was treated for SIN3M0 unresectable colorectal cancer by systemic chemotherapy with oxaliplatin. The patient developed anaphylactic shock during the 8th cycle of FOLFOX therapy (after 4 cycles of FOLFOX4 and 3 cycles of mFOLFOX6) 20 minutes after the start of infusion of oxaliplatin. Oxaliplatin infusion was withdrawn immediately and the patient was treated with intravenous epinephrine, hydroxyzine hydrochloride and methylprednisolone. Anaphylactic symptoms resolved in 12 hours. General symptoms also soon improved and the patient was discharged 14 days after the event. Oxaliplatin is a third-generation platinum salt that is particularly effective for treatment of gastrointestinal cancers. However, the increased use of this drug has shown that it can generate hypersensitivity reactions, including anaphylactic shock. In this case, we were able to save the patient by rapid treatment of oxaliplatin-induced anaphylactic shock.

Key Words: Oxaliplatin, Anaphylactic Shock, FOLFOX, Colorectal Cancer, Hypersensitivity Reaction.

Introduction

Oxaliplatin is a third-generation platinum salt that is particularly effective for gastrointestinal cancers. Oxaliplatin is also useful for treating advanced unresectable colorectal cancer when used together with adjuvant therapy of 5-fluorouracil (5-FU) and leucovorin (LV), a treatment regimen known as the FOLFOX protocol. Patients treated with this regimen have a median survival period of 16 months and a 45.5% response rate. According to WHO criteria, use of oxaliplatin alone gives a response rate of 10% in cases that are resistant to 5-FU and 27% in previously untreated cases[1].

Oxaliplatin is well known to induce neurologic, hematologic, and digestive (nausea, diarrhea, and vomiting) complications, and has been shown to generate hypersensitivity reactions (HSRs) in some

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cases. We define HSRs as unforeseen reactions to a drug that differ from its known toxic symptoms. Oxaliplatin-induced HSRs include facial flushing, emphysema, pruritis, fever, tachycardia, dyspnea, tongue swelling, rash, headache, chills, weakness, burning sensations, dizziness, and edema[2]. Oxaliplatin may also cause severe HSRs such as anaphylactic shock. Symptoms such as burning sensations, flushing, sweating, and dizziness are prodromes of a serious complication such as anaphylactic shock, and it is important not to miss these prodromes. The symptoms usually occur after multiple infusion cycles. When a hypersensitivity reaction occurs, oxaliplatin infusion should be halted immediately and replaced with antihistamine drugs and low-dose corticosteroids. Here, we report a case of life-threatening oxaliplatin-induced anaphylactic shock in which the patient was saved by rapid treatment.

Case Report

The patient was a 74-year-old male who had suffered from asthma from the age of 62 years old and had also undergone surgery for cataracts. In January 2007, he felt discomfort during excretion and was examined by colonoscopy, which revealed a huge tumor in the sigmoid colon. We were concerned that complete resection could not be performed safely because the tumor had invaded the urinary ducts and caused obstructive colitis. Thus, we performed a transverse colostomy to relieve the intestinal pressure and inserted DJ catheters in the urinary ducts.

The patient was then treated for SIN3M0 unresectable colorectal cancer by systemic chemotherapy using the 5FU/LV regimen (Fig. 1). However, despite six cycles of this regimen, the tumor continued to progress. The 5FU/LV regimen was discontinued and replaced by a FOLFOX4 regimen. After four cycles of this regimen, the tumor exhibited a partial response based on assessment using RECIST criteria. The patient then received two cycles of mFOLFOX6, after which we determined that the original lesion had decreased in size and its invasiveness had been eliminated. Consequently, Hartmann's operation was performed, and this revealed that the main tumor was indeed reduced. An intraoperative frozen test of ascites was class Ⅱ, but fibrosis surrounding the tumor was severe and the definitive tissue pathological diagnosis was RM1. The other pathological diagnoses were adenocarcinoma, tubular, tub2, type5, 55×40 mm, SE, N0, Stage Ⅱ, ly0, v0, PM0, DM0, and Chemo effect Grade 2. Therefore, the surgical margin was judged to be positive, leading to continuation of chemotherapy with mFOLFOX6.

In total, the patient tolerated 7 cycles of FOLFOX treatment without exhibiting any toxic reactions except grade 1 peripheral neuropathy and nausea. Allergic reactions to the chemotherapy drugs were not observed. However, during the 8th FOLFOX infusion, and despite pretreatment with steroids and an H1 inhibitor (which was given before every FOLFOX cycle), the patient developed a grade Ⅲ HSR about 20 minutes after the start of oxaliplatin infusion. The patient had shortness of breath, symptomatic bronchospasm, nausea, sweating, and an intense rash on his chest and back. On examination, he was pale, cyanotic, and had a temperature of 36.7°C. Blood pressure dropped to 60 mmHg and the pulse rate was 40 bpm.

Oxaliplatin was discontinued immediately, and 500 mg methylprednisolone, 500 mg hydrocortisone, 0.5 mg atropine, and 1 mg epinephrine were administered intravenously, in addition to oxygen and intravenous colloidal fluid. The patient was hospitalized and transferred to the intensive care unit (ICU), where he stayed for two days. The primary result of blood gas analysis in the ICU was pCO_2/pO_2

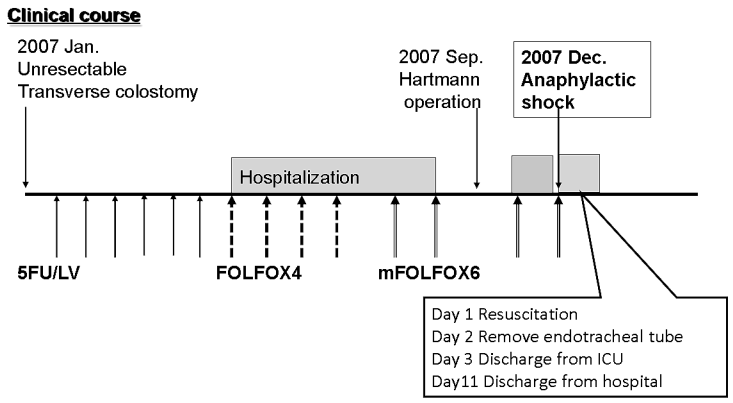

Fig. 1. The patient was treated for unresectable colorectal cancer with systemic chemotherapy using the 5FU/LV regimen (6 cycles). However, the tumor continued to progress and the FOLFOX4 regimen was started (4 cycles). The tumor showed a partial response and the patient then received two cycles of the mFOLFOX6 regimen. The original lesion was reduced in size and its invasiveness was eliminated. Hartmann's operation was performed, but the surgical margin was suspected to be positive. The patient continued to receive chemotherapy with mFOLFOX6, but developed a grade Ⅲ HSR during the 8th FOLFOX infusion.

=53/606, BE/HCO_3=−9.2/19.3, FiO_2 1.0. His vital signs had fully recovered at 12 hours after the incident and the endotracheal tube was removed on the next day. Two weeks later, he was discharged. He has not received oxaliplatin treatment since this incident and is currently alive without recurrence.

Discussion

The incidence of oxaliplatin-induced hypersensitivity reactions (HSRs) has risen recently because of increased clinical use of oxaliplatin for both adjuvant treatment and treatment of metastatic colorectal cancer[2]. Oxaliplatin-induced HSRs have been reported to occur in a substantial minority of patients (12%), but less than 0.55% of oxaliplatin-treated patients develop anaphylactic reactions[3]. Among the HSRs induced by oxaliplatin, patients may experience facial flushing, emphysema, pruritis, fever, tachycardia, dyspnea, tongue swelling, rash, headache, chills, weakness, burning sensations, dizziness, and edema. Even if the symptoms are initially mild, it is possible that a life-threatening anaphylactic reaction could follow. Thus, careful monitoring of patients is required during oxaliplatin treatment and physicians should be prepared to provide appropriate treatment as soon as signs of an anaphylactic reaction appear.

The notable features of oxaliplatin-induced HSRs are that they start after several cycles of chemotherapy and occur unpredictably. In our case, the patient underwent seven courses of oxaliplatin treatment without manifesting any serious adverse events before developing life-threatening anaphylactic shock. A literature search revealed several other reports of allergic reactions associated with oxaliplatin[4-11] (Table 1). In many of these cases, the patients developed anaphylactic shock after several cycles of oxaliplatin[12-16]. In addition, in a Phase Ⅱ study of 46 patients with colorectal cancer who were treated with the FOLFOX regimen, one patient developed anaphylactic shock during the sixth

Table 1. Reported cases of hypersensitivity reactions to oxaliplatin.

	Age	Sex	Lesion	Cycle Number of Incident	Symptoms
Case1[4]	69	M	Recurrent colon cancer	FOLFOX4(8) FOLFIRI(8) FOLFOX4(2nd)	dyspnea blood pressure reductions
Case2[5]	50	M	Sigmoid colon cancer Liver/Lung metastasis	FOLFOX4(9th)	face flash dyspnea
Case3[6]	52	F	Sigmoid colon cancer	FOLFOX4(7th)	dyspnea
Case4[6]	46	F	Rectal cancer	FOLFOX4(9th)	systemic wheal reaction
Case5[7]	63	M	Appendix cancer Liver/Lung metastasis	FOLFOX4(9) FOLFIRI(21) FOLFOX4(2nd)	anaphylaxy
Case6[7]	71	M	Rectal cancer Liver/Lung metastasis	FOLFIRI(18) FOLFOX6(14th)	anaphylaxy
Case7[8]	unknown	unknown	Colon Cancer	FOLFOX4(8th)	anaphylaxy
Case8[9]	65	M	Rectal cancer	mFOLFOX6(6th)	anaphylaxy
Case9[10]	53	M	Colon Cancer	FOLFOX4(10th)	anaphylaxy
Case10[11]	62	M	Rectal cancer Liver/Lung metastasis	FOLFOX4(5th)	anaphylaxy
Our Case	74	M	Sigmoid colon cancer	FOLFOX4(4) mFOLFOX6(4th)	anaphylaxy

cycle, after exhibiting no symptoms in the preceding cycles. These reports also showed that anti-allergic steroids were ineffective for preventing the development of anaphylactic shock[3)17)18)]. Our patient also developed anaphylactic shock despite administration of anti-allergic steroids before each treatment.

The pathophysiology of oxaliplatin-induced HSRs is still unclear. As mentioned above, HSRs to oxaliplatin develop after patients receive several cycles of treatment, suggesting a sensitization process. These reactions, including bronchospasm and skin rash, are generally classified as type Ⅰ hypersensitivity due to the rapid appearance of symptoms after infusion[19)20)]. It has been suggested that platinum compounds may act as superantigens to induce T-cell expansion and subsequent cytokine (IL-6, TNF-α) release[21)]. Another possible mechanism is binding of platinum compounds to major histocompatibility complexes and induction of an immune response[22)]. There may be common features of HSRs with idiosyncratic drug reactions (IDRs), which are reported as adverse drug reactions. A major characteristic of IDRs is the delayed time to onset. With very few exceptions, there is a delay of a week or more in onset of these reactions following primary exposure to a drug. Several hypotheses have been proposed for involvement of the immune system in the mechanism of IDRs, including immune-mediated reactions similar to the mechanisms mentioned above for platinum compounds. Serotonin may also play a role in the mechanism of anaphylactic reactions based on animal models of anaphylaxis[23)24)].

Intravenous fluid treatment, oxygenation, and monitoring are generally important in treatment of shock. Anaphylactic shock is diagnosed when skin rash onset occurs with a so-called ABCD abnormality, where A refers to the airway (abnormal laryngeal edema in anaphylactic shock), B indicates breathing (asthma symptoms), C refers to circulation (abnormal vital signs), and D indicates

digestive symptoms (vomiting, diarrhea, stomach ache). Our case clearly showed skin rash and B and C abnormalities. In such cases, intravenous administration of a large volume of fluid and intramuscular injection of epinephrine should be performed as a top priority. Steroids and antihistamines do not have immediate effects, but are recommended treatment. All of these drugs were used in our case and the patient quickly recovered from shock.

Several reports suggest that oxaliplatin should not be reintroduced if an initial mild HSR is observed, since anaphylactic shock is a life-threatening emergency[2]. However, it is also desirable for patients with gastrointestinal tumors to be treated with oxaliplatin for as long as possible to reduce the tumor growth. Several authors have recommended injection of oxaliplatin with a longer infusion time when patients who showed mild reactions are re-exposed to oxaliplatin[2)17)]. In a retrospective analysis of 124 patients who received oxaliplatin infusion over 2 h, Brandi et al. found 17 cases with HSRs to oxaliplatin[14]. After pre-treatment with steroids and antihistamines, 6 of the 17 patients were re-exposed to oxaliplatin in a 6 h infusion. One patient did not exhibit any further reactions, but 5 of the 6 patients had further HSRs. However, none of these cases developed anaphylactic shock. It has also been suggested that a desensitization protocol after an HSR may be effective for continuation of chemotherapy without an adverse drug reaction, but the tolerated dose of oxaliplatin after this protocol was lower than the required clinical dose and the condition of the patient worsened[25]. These reports indicate that it is difficult to determine the best course to take when a patient exhibits a reaction to oxaliplatin. This decision is made even more difficult if oxaliplatin therapy is effective for the tumor. Even if continued chemotherapy is possible without a HSR, loss of control of the tumor may imperil the patient.

In the case reported here, oxaliplatin was infused at 75 mg/hour for 2 h. Upon development of anaphylactic shock, oxaliplatin was quickly discontinued and steroids and drugs that improved circulation were administered intravenously. The patient is currently alive without recurrence. This case provides a reminder that drug-induced symptoms such as flushing and dizziness should be noted as potential indicators of a more severe reaction during chemotherapy with oxaliplatin.

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〈和文抄録〉

オキサリプラチンによる重症過敏反応

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オキサリプラチンは消化器癌に有効で，現在標準治療として使用される第3世代白金製剤である．しかし，その使用頻度の増加に伴い，アナフィラキシーショックを含む，過敏反応の報告が散見される．我々は，SIN3M0 Sage Ⅲb の切除不能進行結腸癌と診断した74歳の男性に対し，オキサリプラチンを用いた全身化学療法を施行した．症例は合計で8クール目のオキサリプラチン治療施行の最中にアナフィラキシーショックを呈した．オキサリプラチンは直ちに中止し，エピネフリン，塩酸ハイドロキシジン，メチルプレドニゾロンを使用し，蘇生救命された．ICU 入室管理となったが，症状はすぐに改善され，症例は14日後に退院となった．今回，オキサリプラチンによって引き起こされたアナフィラキシーショックを呈した一例を経験したので，報告する．

キーワード：オキサリプラチン，アナフィラキシーショック，FOLFOX，大腸癌，重症過敏反応．