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SHORT COMMUNICATION

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Two potential mechanisms of oxaliplatin-induced haemolytic anaemia in a single patient

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Abstract Only two patients with adequately documented oxaliplatin-induced autoimmune haemolytic anaemia have previously been reported. We report here a third patient with an immune-haematological finding favouring a bispecific mechanism (immune-complex and penicillin type) of oxaliplatin-induced haemolysis.

Keywords Colorectal cancer · Oxaliplatin · Haemolytic anaemia

Introduction

Oxaliplatin (L-OHP) is a platinum compound with activity against a broad range of tumours. Recently, L-OHP has been approved by the FDA in combination with 5-fluorouracil (5-FU) and folinic acid (FA) for metastatic colorectal cancer [4]. Common side effects are cumulative sensory neuropathy, diarrhoea, mild myelosuppression and mucositis. We report here a patient with L-OHP-induced autoimmune haemolytic anaemia (AIHA) along with the pertinent immune-haematological findings.

Case report

In August 2001 a 51-year-old woman was admitted with unresectable metastases of rectal cancer. Palliative chemotherapy consisting of a 2-h infusion of L-OHP 85 mg/m^2 (on days 1, 15 and 29; repeated on day 57), and weekly 24-h infusion of 5-FU 2000 mg/m^2 and sodium-FA 500 mg/m^2 (mixed with 5-FU in one pump; repeated on day 57) was commenced on 15 August 2001. Dexamethasone (8 mg) and ondansetron (8 mg) were added to L-OHP as antiemetic prophylaxis. A total of five cycles were administered until May 2002 resulting in partial remission of liver metastases. No adverse events occurred. On 28 May 2002, 6 days after the last L-OHP administration, the patient presented with a decrease in haemoglobin (Hb) from 11.1 g/dl (22 May) to 8.4 g/dl. Gastrointestinal haemorrhage was excluded. Lactic dehydrogenase (LDH) activity was slightly elevated (433 U/l) and haptoglobin was absent. Intercurrent haemolysis was suspected but Hb increased without transfusion of packed blood cells to 10.4 g/dl and chemotherapy was continued on 25 June. The patient received 155 mg L-OHP (2-h infusion) and 3760 mg 5-FU as a 24-h continuous infusion. During the infusion she vomited twice despite treatment with ondansetron and dexamethasone and reported mild back pain. At home 4 h after the start of the treatment she noticed dark-coloured urine. On 26 June, she developed jaundice lasting for 2 days.

The patient did not present until 2 July. Blood values on that day were: Hb 6.7 g/dl, platelets 104,000/μl, bilirubin 16.1 μmol/l, and LDH 498 U/l. Haptoglobin was within the normal range. Creatinine was 631 μmol/l, and blood urea nitrogen was 38 mmol/l. No fragmentocytes were seen in the blood smear. Drug-dependent haemolysis was suspected. DAT (Coomb's test) was strongly positive with maximal coating of the erythrocytes with IgG and C3d. Elution of the antibodies was negative. Assessment of drug-induced haemolysis was carried out as follows:

1. Untreated test erythrocytes + patient's serum: no agglutination
2. Untreated test erythrocytes + patient's serum + L-OHP: strong agglutination
3. Test erythrocytes previously treated with L-OHP + patient's serum: moderate agglutination
4. Test erythrocytes + AB serum of healthy donor + L-OHP (negative control): no agglutination
5. Test erythrocytes previously treated with L-OHP + AB serum of healthy donor: no agglutination

The patient was treated with i.v. prednisone 1 mg/kg body weight. Hb increased to 10.5 g/dl within 10 days of treatment and creatinine normalized. The patient was treated with oral prednisone until October 2002. Treatment for colorectal cancer was subsequently continued solely with 5-FU and FA. On 19 October, DAT was negative, and immune-haematological monitoring of drug-induced haemolysis showed the same results as in July: untreated test erythrocytes + patient's serum + L-OHP resulted in strong agglutination and test erythrocytes previously treated with L-OHP and patient's serum showed moderate agglutination.

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Discussion

We report a 51-year-old female patient with metastatic colorectal cancer treated with L-OHP who developed severe AIHA after a cumulative dose of 1350 mg/m^2. The intravascular haemolysis was mainly due to complete activation of complement. In view of the clinical presentation (rapid onset and acute renal failure) and according to the immune-haematological results, predominantly immune-complex type AIHA appeared to be the most probable mechanism. Nevertheless, the patient's serum showed moderate agglutination with test erythrocytes that had been pretreated with L-OHP. Thus, in addition, a penicillin type comechanism must be considered. Thrombocytopenia was only mild and antibodies against platelets were not found.

Cisplatin and carboplatin have been reported to induce AIHA [5, 6]. There are to date four previous reports of haematological emergencies after L-OHP administration. Two patients with haemolysis and thrombocytopenia after L-OHP administration in Norway have been described, but appropriate immune-haematological assessment had not been carried out [7]. A patient with fatal Evan's syndrome has also been reported [2]. In this patient, the eluted antibodies reacted with all erythrocytes. This finding does not match drug-induced AIHA. Garufi et al. reported a female patient with AIHA after high cumulative doses of L-OHP (1580 mg/m^2) [3]. The immune-haematological workup of this patient was typical of penicillin-type AIHA. Desrame et al. reported a patient with fatal haemolytic anaemia which the authors attributed probably to an immune-complex type AIHA [1]. Both the latter patients and the patient reported here were women. They developed AIHA after treatment with L-OHP for several months. The onset of haemolysis was rapid, and was accompanied in two patients by acute renal failure. Retrospectively, the decrease in Hb in our patient 3 weeks before the severe episode reported here may be interpreted as mild haemolysis and the routine use of dexamethasone for antiemetic treatment may have prevented fatal AIHA in this patient.

To sum up, all three patients with AIHA induced by L-OHP whose blood had undergone adequate immunological examination were women and had received high cumulative doses of L-OHP. The patient described in this report was suspected to have developed AIHA by two mechanisms: immune-complex type seems more probable than penicillin type, but the latter must be considered a possibility.

Immediate treatment with corticosteroids appears to be the most appropriate treatment in cases of L-OHP-induced AIHA. In view of the expanded use of L-OHP after approval for colorectal cancer by the FDA, and given the broad spectrum of antitumour activity of L-OHP that makes this drug an ideal candidate for use in other tumour types, a growing number of haematological emergencies after L-OHP might be expected. Oncologists should be aware of this rare but life-threatening adverse event.

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