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Case report

Platin salts-induced hemolytic anemia: cisplatin- and the first case of carboplatin-induced hemolysis

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Anemia is a common side effect of cisplatin, especially after repeated infusions. The primary mechanism is a myelosuppression caused by cisplatin's interference with iron metabolism, resulting in a lower count of red cell precursors. Some authors report a hemolytic anemia similar to penicillin-induced anemia, in which hemolysis is caused by an antiglobulin antibody directed against red cell membrane-bound cisplatin. The authors report two cases of cisplatin-induced anemia and suggest that the immune-complex hypothesis is responsible for hemolysis. The first case of carboplatin-induced hemolysis is also reported. Mechanisms of hemolysis and clinical practice are discussed.

Key words: Anemia, carboplatin, cisplatin, hemolysis, toxicity.

Introduction

Cisplatin is an alkylant agent used alone or in combination chemotherapy for the treatment of various tumors, especially ovarian and testis carcinoma. Cisplatin toxicity is essentially nephrologic and neurologic, and the most constant secondary effects are nausea and vomiting.[1,2]

Hematological toxicity is mild but the appearance of a deep anemia has been described many times and related in some cases to an immunologic mechanism.[3] Carboplatin has comparable activity to cisplatin but is more myelosuppressive and may require the use of hematopoietic growth factors.

Platin salts-induced hemolytic anemia is a rare event and was never reported for carboplatin. We report three cases of hemolytic anemia, two of them related to cisplatin and the first case related to carboplatin.

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Methods

Red blood cells were sensitized with cisplatin and carboplatin as follows: 0.5 ml washed, packed red cells, O Rh(D) positive, were incubated for 1 h at 37°C with 0.5 m solution containing 1 mg cisplatin or carboplatin, 0.5 ml fresh AB sera and 1.5 ml patient sera. In the same experiment, both drug and patient reference solutions were performed with patient sera and drug, respectively.

After incubation, sensitized red cells were washed three times in a saline solution and resuspended at 5% concentration in BFI.

Direct antiglobulin test (DAT) was carried out with polyspecific anti-human globulin (Gel Diamed, France) and monospecific anti-IgG; IgM; C3; C3d; C4 (Plaquette; Gel Diamed). The indirect antiglobulin test (IAT) was carried out with polyspecific anti-human globulin in a plate technique (Sanofi Diagnostic Pasteur, France) and anti-IgG in a test tube technique (Sanofi Diagnostic Pasteur). Anti-cisplatin and anti-carboplatins did not titer.

Patients

Case 1

A 44 year old female was admitted with an extragonadic germ cell tumor, disseminated in lungs. A combination of VP-16 (300 mg/m^2), ifosfamid (1200 mg/m^2), and cisplatin (100 mg/m^2) was administered over five consecutive days every 3 weeks, in addition to bleomycin (30 mg weekly). Four months later, she had partial response of her lung involvement; despite a peripheral neuropathy, no sign of hemolysis was noted. Therefore, she underwent a combination of vepeside (150 mg/m^2), ifosfamid (600 mg/m^2) and carboplatin (450 mg/m^2) over 3 days at 4 week intervals. With-

in 3 weeks after the first course of chemotherapy, the hemoglobin, leucocyte, platelet and reticulocyte counts were, respectively, 92 g/l, 1.9×10^9/l, 200×10^9/l and 196×10^9/l. Serum lactic dehydrogenase activity (LDH, Nl < 370 U/l) was 1000 U/l. Neither bilirubin nor haptoglobin assays were performed. A second carboplatin course was administered. Four weeks later hemoglobin was 127 g/l, reticulocytes were 212×10^9/l, leucocytes were 12.3×10^9/l, platelets were 300×10^9/l, bilirubin was normal and LDH was 804 Ul/l. Although DAT and IAT were negative, the latter became positive with adjunction of both cisplatin and carboplatin. Despite this result, carboplatin was followed without worsening of the hemolysis.

Case 2

A 56 year old female was admitted with a T4dN+M0 breast cancer. Hormonal receptors were positive. She received six courses of neo-adjuvant FAC chemotherapy associated with tamoxifen (30 mg daily). Then she had a radical mastectomy and local radiotherapy, followed by three additional FAC courses. Three years later she was found to have a metastatic dissemination to lung, liver and bone. She underwent a combination with cisplatin (100 mg/m^2) and 5-fluorouracil (5-FU) (5000 mg/m^2) given over five consecutive days every 3 weeks. Within 3 weeks after the fifth course she developed pancytopenia with 1.5×10^9/l leucocytes, 27×10^9/l platelets and 74 g/l hemoglobin. The concurrent anemia was regenerative with 200×10^9/l reticulocytes. Both DAT and IAT were negative. Nevertheless, the IAT became positive with adjunction of cisplatin and remained negative with carboplatin. The treatment continued with carboplatin (300 mg/m^2) over 3 days, instead of cisplatin, without any recurrent hemolysis. Three courses later, the antiglobulin test with carboplatin and cisplatin remained negative.

Case 3

A 49 year old female was admitted with loco-regional recurrent breast cancer (T2N2M0), diagnosed 3 years earlier. She received six cycles of adjuvant FAC chemotherapy, local radiotherapy and tamoxifen (30 mg daily). Two years later, she developed liver and bone metastasis. Therefore, she was treated with cisplatin (100 mg/m^2) and 5-FU (50.0 mg/m^2) over five consecutive days every 3 weeks. After the first course, she developed a regenerative anemia with 83 g/l hemoglobulin, 2.1×10^9/l leucocytes, 58×10^9/l platelets and 140×10^9/l reticulocytes. Haptoglobin, bilirubin and LDH remained normal. Both DAT and IAT were negative, but became positive with adjunction of cisplatin and remained negative with carboplatin. The patient underwent the same combination, but cisplatin was replaced by carboplatin (300 mg/m^2). Hemolysis did not recur. After five course, both DAT and IAT remained negative, even with cisplatin or carboplatin adjunction.

Discussion

The occurrence of anemia during cisplatin therapy has been frequently reported since the first clinical trials; this anemia is usually mild but increases with the number of chemotherapy cycles. Anemia is a common consequence of platinum salts toxicity. Its effects on red blood cell production may be delayed and cumulative. Some authors report the mechanism of cisplatin-induced anemia as an interference with iron metabolism at the erythroid precursors levels.[3,4] The decrease in number of red line precursors would bring about a diminution in the iron available for the synthesis of hemoglobin at the medullary level. Recently, inadequate endogenous erythropoietin levels were demonstrated as the main characteristic of anemia of cancer and could be induced by myelosuppressive chemotherapy, including platinum-containing regimens.[5,6]

Hemolytic anemia with antiglobulin, first described by Getaz *et al.*[7], has been reported in a few patients treated with cisplatin.[8–13] A sudden decrease of hemoglobin level when using cisplatin should raise a suspicion of hemolysis, as shown in our experience.[13] The mechanism of sensitization to platinum salts remains unclear.

Pharamacologic data indicates that cisplatin is cleared rapidly from plasma after intravenous injection, but cisplatin clearance proceeds much more slowly thereafter due to binding to plasma proteins and erythrocytes.[2] Previous data suggests that the mechanism appears to be similar to that of penicillin-induced hemolysis, for example an immune hemolysis with antibodies targeted to platinum fixed onto the erythrocyte membrane.[7,14] In these cases, the DAT was positive, of IgG type and became negative 4–5 weeks after drug withdrawal. In all our cases, the DAT was negative, but the IAT was positive only if incubated with cisplatin. A possible explanation is that biological investigation was performed at least 15 days after cisplatin infusion,

whereas the DAT is only positive during and for 48 h after cisplatin infusion.[6] Once the responsible drug had been withdrawn, the decrease in hemolytic biological features is as rapid as the DAT negation. This may explain the normality of LDH, bilirubin and haptoglobin in cases 2 and 3.

However, the authors suggest another drug-related hemolysis mechanism: the immune-complex hypothesis. In this hypothesis, cell destruction is due to the formation of high-affinity antibodies directed against a stable complex of the drug and some soluble non-cellular macromolecule, such as a plasma protein. Salama and colleagues have recently proposed a coherent explanation.[14] The immune response in drug-induced hemolysis is initiated by a primary interaction of the drug and/or metabolites with constituents of the blood cell membrane. The interaction (loosely or stably bound) may by chance alone create a 'neoantigenic' structure that may provoke the production of drug-dependent antibodies and/or autoantibodies. Of major interest is case 1, the first case of carboplatin-induced hemolysis, where the IAT is positive with the two platinum salts. In the other cases when cisplatin-induced hemolysis, the IAT is always positive with cisplatin but never with carboplatin. Our hypothesis is that 'neoantigens' created by carboplatin are included as a part the cisplatin-induced 'neoantigen'. This may explain the fact that cross-reactivity is observed only in the case of carboplatin-induced hemolysis.

Giving cisplatin in a continuous infusion for a few days,[3,11] as in our cases, or in a single infusion for a few hours[1] makes no difference to the emergence of red blood cell sensitization. The occurrence of cisplatin-induced hemolysis does not necessarily mean that other platinum sales should be prohibited. In cases 2 and 3, as previously reported,[13] employment of carboplatin after cisplatin sensitization did not lead to any cross-reaction. In the same way, Creaven *et al.*[14] reported one patient with a cisplatin-induced hemolysis who tolerated iproplatin. Of major interest is case 1, where a patient developed hemolysis due to carboplatin. Indeed carboplatin-induced hemolysis has not been reported to date. In this case, we noted a cross-reaction in biological tests with cisplatin.

Despite this latter case, we propose that cisplatin-induced hemolysis should not justify final proscription of other platinum salts. The lack of cross-reaction with carboplatin indicated that carboplatin could be used. In some cases, as in case 1, following with the same platin compound was not associated with worsening of hemolysis. Carboplatin administration thus implicates strict monitoring of clinical and biological status during and after the infusion.

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