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Positive direct antiglobulin test in a pediatric patient following high-dose cisplatin

G. Cinollo[1], G. Dini[2], E. Franchini[1], E. Lanino[2], F. Sindaco[1], and A. Garaventa[2]

[1] Blood Bank "Giannina Gaslini" Children's Hospital and
[2] Department of Pediatric Haematology/Oncology, "Giannina Gaslini" Children's Hospital, Genova, Italy

Summary. A positive direct antiglobulin test (DAT) and hemolitic anemia are uncommon side effect of cisplatin (CDDP) therapy. A 9-year-old girl treated for extraosseus Ewing's sarcoma with a multiagent regimen, including 200 mg/m^2 CDDP preceded by vincristine (VCR) and cyclophosphamide (CY), developed a posititve DAT, followed by hemolitic anemia. When CDDP therapy was discontinued, the DAT became negative and no signs of anemia were observed during the maintenance treatment, which included VCR and actinomycin D.

Introduction

cis-Diamminedichloroplatinum (CDDP) is proving to be one of the most encouraging new drugs introduced for the treatment of solid tumors [8], even in pediatrics [1]. Nephrotoxicity is commonly identified as the dose-limiting factor, with other side effects including gastrointestinal toxicity, myelosuppression, ototoxicity, and neurotoxicity. Other important side effects have less frequently been observed, including anaphylactic reactions, peripheral neuropathies, cardiotoxicity, and hemolitic anemia [9]. The etiopathologic mechanisms that result in CDDP-induced anemia are still unclear [2–5]; however, a peculiarity of the transferrin receptor in the K562 erythroid leukemic cell line may account for a direct effect on hematopoietic precursors [7].

This report concerns a pediatric case of hemolytic anemia with a positive DAT immediately following CDDP therapy.

Case report

A 9-year-old girl with extraosseus Ewing's sarcoma of the pelvis underwent a 5-day therapeutic program including CDDP (200 mg/m^2), preceded by 2 mg/m^2 vincristine (VCR) and 600 mg/m^2 cyclophosphamide (CY) [1]. The entire cycle was repeated every 6 weeks. Before and after the first course of treatment, the hemoglobin concentration was 9 g/dl; the patient received one unit of packed red cells and was referred to a local hospital. Three weeks after the last dose of CDDP, the hemoglobin concentration dropped to 6.5 g/dl: reticulocyte count was 3% (cells/mm^3), including 1% nucleated red cells; serum lactic dehydrogenase activity was 715 units/l, haptoglobin 110 mg/dl, and bilirubin 1.4 mg/dl. Two further units of packed red cells were transfused and a second course was given as warranted by the protocol. At this time the hemoglobin concentration was 9.7 g/dl; the patient did not show any signs of hemolysis during treatment. Following the last dose of CDDP, the hemoglobin concentration was 9.5 g/dl; the patient received 2 units of packed red blood cells and was discharged. Two weeks later, the hemoglobin concentration was 7.7 g/dl; 1 unit of packed red blood cells was transfused. The patient subsequently underwent surgery and the mass was completely removed. During the maintenance treatment, including VCR, CY, and actinomycin D, no transfusion treatment was required.

Materials and methods

DATs were carried out during and after both courses of treatment.

Red blood cells were sensitized with CDDP (RBC-CDDP) as follows: 0.5 ml washed, packed red cells, O Rh (D)-positive, were incubated for 1 h at 37° C with 1 ml solution containing 1 mg CDDP, washed 3 times in saline solution, and resuspended to a 5% concentration in saline solution.

Red-cell eluates were prepared according to the method of Rubin [6]. Direct and indirect antiglobulin tests (D/IAT) were carried out with polyspecific antihuman globulin (AHG) and monospecific anti-IgG (Ortho Diagnostic, Raritan, NJ, USA) and anti-C3d (Biotest, Frankfurt/M, FRG). Polyspecific antihuman globulin, anti-IgG, and anti-C3d DATs were performed on samples of the patient's cells that were anticoagulated with EDTA. Antibody screening cells and identification panels were obtained commercially (Ortho Diagnostic, Raritan). Anti-CDDPs were titrated by means of a standard, twofold serial saline dilution through the IAT phase with RBC-CDDP.

Results

During the first course of treatment, the DAT was positive with AHG (+++) and monospecific anti-IgG (+++), but negative with monospecific anti-C3d. Both the eluates and IAT were negative.

The patient had received a blood transfusion prior to the developmen of hemolysis, but we can exclude an anti-

Offprint requests to: G. Dini, Department of Pediatric Hematology/Oncology, "Giannina Gaslini" Institute, Via 5 Maggio 39, I-16148 Genova, Italy

body specificity versus an infrequent antigen, as both the serum and the eluate tested with donor red cells were negative. On the other hand, when RBC-CDDPs were used the IAT was strongly positive with AHG or with monospecific anti-IgG, but not with anti-C3d. Anti-CDDP titration rose to 1/32, against RBC-CDDP. The patient's serum, tested on commercial panels previously sensitized with CDDP, was panagglutinate with AHG or with monospecific anti-IgG.

Before the second course of treatment, the DAT and IAT were both negative; the IAT, however, was positive with RBC-CDDP. The DAT became strongly positive (+ + + +) immediately after treatment with CDDP; at the same time, the titer of anti-CDDP free antibodies rose to 1/256. Two days after the last dose of CDDP, the positivity of the DAT was strongly reduced.

Discussion

Cisplatin-induced hemolytic anemia has previously been described [2–5]. DATs may be positive without overt hemolysis [3].

We could not find a particular antigen specificity for the drug carrier after testing the patient's serum with a resolve panel previously sensitized with CDDP.

The fact that during maintenance treatment, including VCR and CY, the patient did not show a positive DAT or hemolitic anemia confirms that our case represents an example of hemolysis induced by CDDP. We suggest that an IgG antibody against red cell membrane-bound CDDP is responsible for the hemolysis, similar to that induced by penicillin; a positive DAT may not be correlated with overt hemolysis and does not necessarily mean that the drug must be discontinued.

Further studies and careful screening of patients receiving CDDP could be useful in assessing the frequency and the mechanism of CDDP-induced anemia.

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