# Efficacy of therapeutic plasma exchange in a severe immune haemolytic anaemia induced by a carboplatin desensitization procedure

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**Key words:** Drug induced immune hemolyticanemia. Immunohematology. Carboplatin. Therapeutic Apheresis.

**Palabras clave:** Anemia hemolítica immune inducida por fármaco. Inmunohematología. Carboplatino. Aféresis terapéutica.

A 37-year-old female was diagnosed at the age of 14 with an ovarian papillary carcinoma, currently at stage IV. She received multiple lines of chemotherapy including two lines of carboplatin in 2000 and 2008.

In 2009, during the administration of the first cycle of carboplatin (third line of treatment),she developed generalized malaise, fever, palmar pruritus and severe dyspnoea. Drug infusion was discontinued; symptomatic treatment was administered, and the patient immediately recovered. She tolerated 5 further cycles of carboplatin with pre-medication (dexchlorpheniramine and 6-Methylprednisolone).

In 2016, she again required carboplatin. Shewas referred to our Allergy Department for an evaluation. Prick and intradermal tests to carboplatin at 1mg/ml were negative.

The first cycle of 395mg of carboplatin was tolerated following a desensitization protocol [1].A 3-solution, 12-step protocol delivered doubling drug doses by step and premedicated with aspirin, prednisolone, cetirizine and montelukast. Following cycles were administered monthly with the same regimen. After the administration of the tenth cycleshe became presyncopal with fading vision. Her blood pressure (BP) was 90/60mmHg, as her baseline BP; she was given serum therapy without improvement. She reported dysthermia and lumbar back pain. She was transferred to the Emergency Department (ED). Of note, the patient did not experienced pruritus, angioedema, dyspnea or other signs of an immediate hypersensitivity reaction.

In ED her oxygen saturation was stable, and she had raised axillary temperature 37,8ºC. Laboratory analysis showed: hemoglobin (Hb) 6.3 g/dL, total bilirubin 3.9 mg/dL and LDH

 
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2052 IU/L. Blood test from previous forty-eight hours showed normalHb 11.2 g/dl, total bilirubin 0.5 mg/dL and LDH 200 IU/L.

She received 3 red blood cell transfusions, she was started on a course of levofloxacin 500mg and methylprednisolone 250mg. She developed an acute bilateral pulmonary thromboembolism48 hours after the carboplatin administration. She was admitted to Intensive Care Unit and treated with fibrinolysis. Cyclophosphamide, rituximab, intravenous immunoglobulin IgG (IVIG), and multiple transfusions of red blood cells were administered reaching a peak Hb level of 9 g/dL. On the following daysHb dropped again to 6.5 g/dL, indicating persistent haemolysis.

Patient's serum was investigated: ABO group was O and Rh type was positive. Liss indirect antiglobuline test (IAT) was also positive. Polyethylene glycol antibody identification test showed an antibody reacting (positive agglutination, score 5) with all the commercially available group O antibody detection red cells. Direct antiglobulin test (DAT) was positive with polyespecific reagent (score 12) and with IgG and IgM reagents (score 12). A positive result of Anti-C3d (score 11) confirmed the activation of complement system. Testing of the serum and the eluate demonstrated an autoantibody and autologous adsorption ruled out the presence of underlying clinically significant alloantibodies. All these initial results determined the patient had haemolytic anaemia of immunological origin.

To determine the drug's involvement in the destruction of the patient's red blood cells an investigation of drug-induced immune haemolysis was pursued. Briefly, a solution of 0.88 mg/ml of carboplatin in phosphate buffered saline at PH 7.0/7.4 was prepared (same as that given to the patient). Patient's red blood cells (RBC) were treated with the carboplatin solution (incubation of carboplatin solution at room temperature and at 37ºC for 1 hour). Haemolysis occurred only when patient's serum was tested with carboplatin treated RBC, but not with untreated (ABO group O donor RBC), thus concluding that patient had carboplatin-induced immune haemolytic anaemia.



 
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Carboplatin half-life is 167 hours (7 days), meaning the drug would be eliminated in 7 half-lives (48 days). Due to the critical situation and the continuous haemolysis it was decided to perform a therapeutic plasma exchange (TPE) with plasma replacement (1900cc).

After the treatment, the patient had a progressive increase on Hb levels; reaching a peak of 11g/dL. She was discharged within 13 days of admission.

Carboplatin is analkylating agent widely used for the treatment of different types of cancer. Its main toxicity is myelosuppression; anaemiais common during the treatment.

Desensitization protocols to chemotherapeutics are used to address hypersensitivity reactions. This protocols are tailored to each individual, and protect against anaphylaxis.

Drug-induced immune hemolyticanemia (DIIHA) is a rare disease with an estimated incidence of 1 per 1 million patients per year [2, 3]. The exposure to a certain drug induces a rapid fall in circulating RBCs via an immune-mediated process [3].

Laboratory findings include anaemia, reticulocyte elevation, hyperbilirubinemia, low haptoglobin and elevated LDH.

This case corresponds to a type II of the Gell and Coombs classification. These reactions are mediated by the interaction of preformed IgG and IgM antibodies with antigens present on the cell surface and other tissue components. There are 7 reported cases of carboplatin-mediated haemolytic anaemia [4-10]. Interestingly there's one publication [4] describing a similar case with a combination of a type I IgE-mediated reaction and a type II IgG-mediated reaction to carboplatin occurring during desensitization. In our case, IgM to carboplatin was also detected and had a severe clinical course requiring TPE.

DIIHA does not appear in any case with the administration of the first cycle**.** Symptoms in all cases are similar and it seems that lumbar pain is characteristic. Anti-IgG and anti-C3 antibodies were found in 6 of the cases [5-9], and our patient was the only one who had anti-IgM antibodies. None of the previous patients received TPE, two died and five presented good evolution.

 
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TPE technique removes large-molecular-weight substances such as antibodies from the plasma. The extraction of plasma is carried out while a replacement solution is being infused; this maintains the volume and the oncotic pressure. The aim is to eliminate preformed antibodies and immunocomplexes to avoid tissue damage.

Considering that DIIHA is a rare condition, this can appear in patients receiving chemotherapy under desensitization schemes. Professionals involved with the administration of this medication should be aware of it.

To our knowledge, this is the second case of DIIHA to carboplatin under a desensitization scheme.

TPE should be taken into consideration as a treatment in patients with severe DIIHA as it showed to be effective in our patient.

**Presented at conferences:**

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**Conflicts of interest**

The authors declare that there is no conflict of interest regarding the publication of this article.

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