Treatment of Mitomycin-C-Associated Hemolytic Uremic Syndrome with Plasmapheresis

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Dear Sir,

We have read with great interest the case report of Garibotto et al. [1], 'Successful treatment of mitomycin C-associated hemolytic uremic syndrome by plasmapheresis', published in this journal recently, so we would like to contribute with our experience in this aspect. Hemolytic uremic syndrome (HUS) is a severe complication that has been associated with mitomycin C (MMC) therapy and is referred to be mostly unresponsive to treatment [2-4].

In the last 2 years we have observed 3 patients affected by HUS associated with MMC therapy which were treated with plasmapheresis. All the patients underwent renal biopsy and met the criteria for the diagnosis of HUS. Plasmapheresis was instituted in addition with corticosteroids. The first patient was a 23-year-old female in whom right hemicolectomy was performed for adenocarcinoma. She received 3 courses of MMC (cumulative dose of 60 mg/m²) and 5-fluorouracil (cumulative dose 2,400 mg/m²). Three months later she developed progressive asthenia. Hematocrit was 21% with 2.8% reticulocytes, platelets $15 \times 10^9/l$ ($15 \times 10^9/\mu l$), lactate dehydrogenase (LDH) 925 IU/l and haptoglobin 0.106 g/l (10.6 mg/dl). Schistocytes were found in the peripheral blood smear. Creatinine was 185.6 $\mu\text{mol/l}$ (2.1 mg/dl) and mild proteinuria was found. She received prednisone (2 mg/kg day) for 3 weeks with no improvement. Plasmapheresis was instituted when creatinine was 486 $\mu\text{mol/l}$ (5.5 mg/dl) and she did not improve after 34 sessions dying of intrabdominal hemorrhage.

The second patient, a 56-year-old man, had a rectal adenocarcinoma. Surgical excision and 4 courses of MMC (cumulative dose 80 mg/m²) and 5-fluorouracil (cumulative dose 2,400 mg/m²) were performed. Two months later he was admitted for progressive dyspnea. Hemoglobin was 4.03 mmol/l (6.5 g/dl) with 3.7% reticulocytes, platelet count $52 \times 10^9/l$ ($52 \times 10^9/\mu l$) and LDH 630 IU/l. Creatinine was 141.44 $\mu\text{mol/l}$ (1.6 mg/dl) and the urinary sediment was normal. Treatment with prednisone (2 mg/kg/day) was initiated with clinical and biological improvement. Two months later, although on treatment with prednisone (15 mg/day), he was admitted because of worsening of the HUS. So, plasmapheresis was instituted and the patient improved after 17 sessions, remaining with mild renal failure. Being on treatment with dipyridamole he developed progressive renal failure, requiring hemodialysis 14 months later.

The third patient presented a satisfactory evolution with plasmapheresis. She was a 49-year-old woman who underwent right hemicolectomy for adenocarcinoma. Twelve months later an ileotransversostomy was performed because of local recidiva. She received 4 courses of chemotherapy with MMC (cumulative dose 80 mg/ m²) and 5-fluorouracil (cumulative dose 2,400 mg/m²). Forty days later she was admitted because of exertional dyspnea, arterial hypertension and oliguria. Hemoglobin was 4.52 mmol/l (7.3 g/dl), haptoglobin 0.30 g/l (30 mg/dl), and a large number of schistocytes were observed in the peripheral blood smear. Platelet count was $58 \times 10^9/l$ ($58 \times 10^9/mm^3$), LDH 800 IU/l, creatinine 309.4 $\mu\text{mol/l}$ (3.5 mg/dl), proteinuria 1.7 g/day and microhematuria was found. Treatment with methylprednisolone (1 mg/kg/day), aspirin (1 g/day) and early plasmapheresis were initiated. After 9 sessions she improved clinically and biologically, remaining asymptomatic with near-normal renal function [creatinine values of 132.6 $\mu\text{mol/l}$ (1.5 mg/dl) and platelet count 2 years later. Treatment of HUS associated with MMC therapy has been as yet unsuccessfully. Various therapies have been tried with at best inconsistent results. The low number of

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patients with this syndrome that have been treated with 2 plasmapheresis preclude analyses for statistical significance. Nevertheless, corticosteroids associated with plasmapheresis are apparently the most effective [2–4], mainly if they are instituted early in the course of the disease [3], as demonstrated by our experience.

Plasmapheresis has been reported to reverse the hematologic manifestations of the microangiopathic process, but not the renal involvement [1,3,5,6]. It is suspected that HUS associated with MMC has a wide spectrum of severity, ranging from mild affection, perhaps misdiagnosed, to most severe forms [2]. We believe, however, in agreement with Garibotto et al. and other authors [7], that plasma exchange in association with corticosteroids should be tried early in patients affected with this syndrome, given that they present mostly a bad outcome with other therapies.