Treatment of POEMS syndrome with bevacizumab

We report a case of POEMS syndrome which relapsed six years after autologous peripheral blood stem cell transplantation. According to encouraging data published recently, we treated the patient with cyclophosphamide, dexamethasone and the VEGF-antibody bevacizumab. After an initial improvement, the subsequent course was complicated by severe adverse events leading to multiorgan failure and death. This dramatic decline highlights the need for further investigation before using bevacizumab in patients with POEMS syndrome.

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The pathophysiology of POEMS syndrome (acronym for polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes) is still not fully understood. It is a rare plasma cell disorder and it has been suggested that increased serum levels of vascular endothelial growth factor (VEGF) cause its development.[1] Few studies have presented data on the efficacy of targeting VEGF with the selective antibody bevacizumab as a therapeutic approach. Badros *et al*. described two patients who were treated successfully with bevacizumab.[2,3] In a similar clinical situation, a 49-year old man was first diagnosed in 1998 with POEMS syndrome. He initially received melphalan and prednisone, irradiation of osteosclerotic bone lesions in the pelvis and thereafter high-dose dexamethasone, plasmapheresis and intravenous immunoglobulins without an objective clinical benefit. Autologous peripheral blood stem cell transplantation following high-dose melphalan led to stabilization of the disease in 1999. His condition remained stable for six years.

In February 2006, he presented with progressive distal and symmetric sensory and motor neuropathy and symptoms of heart insufficiency with dyspnoea and peripheral oedema. Echocardiography demonstrated a reduced ejection fraction and a moderate pulmonary hypertension. Bone marrow aspiration showed a plasma-cell count <10% with normal morphology. Computed tomography revealed cardiomegaly and hepatosplenomegaly. The two previously irradiated pelvic lesions had remained unchanged over the previous six years and there were no signs of new osseous manifestations. The patient had large effusions in the pericardium, pleura and peritoneum. Thyroid stimulating hormone (TSH), pro-brain natriuretic peptide (pro-BNP), β-2 microglobulin and interleukin (IL)-6 were elevated (Table 1). Monoclonal protein type IgA-λ fraction was only detectable by immunofixation. Tumor necrosis factor (TNF) and IL-2 levels were within normal range. Hemoglobin was slightly decreased, with normal platelet and white blood cell counts. All symptoms indicated of a relapse.[4]

The patient received diuretics, ACE blocker, low dose β blocker and thyroid hormone. Since he met criteria for highly active disease, we started a combined immunochemotherapy with bevacizumab, intravenous cyclophosphamide and oral steroids based on the response reported by Badros *et al*. After two courses, a clinical improvement was seen with resolution of the effusions and improvement of the left ventricular function. In addition, levels of pro-BNP, IL-6 and β-2 microglobulin decreased. Baseline concentration of VEGF was not assessed and levels were elevated only moderately five days after onset of therapy. However, they decreased further during the next course (Table 1).

After the fourth course of immunochemotherapy the patient developed refractory diarrhea and generalized oedema with widespread swelling of the skin. Echocardiography showed a normal left ventricular function, but a worsening of the pulmonary hypertension with dilated right heart cavities. Laboratory results indicated a systemic inflammation without clinical signs or microbiologic confirmation of an underlying infection. Parenteral nutrition was necessary and he received sildenafil and iloprost. Cardiopulmonary instability required the administration of fluids and catecholamines in the netx course. Nonetheless, his condition worsened and he died after multiorgan failure. The autopsy revealed a chronic neuropathy and obliteration of the small pulmonary arteries next to generalized edema and enlargement of the organs with signs of diffuse vascular damage. Furthermore, an increase in κ- and λ-positive cells in the bone marrow was seen without evidence of monoclonality.

In a report by Straume *et al*.,[3] a dramatic clinical course was described after onset of bevacizumab therapy in a patient with similar clinical features leading to the patient`s death.[2] The authors hypothesized that rapid

Table 1. Laboratory and clinical parameters in the course of therapy.

	10.03.2006	*23.03.2006*	*12.04.2006*	*12.05.2006*	*09.06.2006*
Plasma cells, % BM	< 10	–	–	–	–
IL-6, ng/L	10.8	8.4	9.6	5.6	11.5
β2 MG, mg/L	10.5	5	5.9	6	14.3
VEGF, pg/mL	97*	53	17	20	77
Pro-BNP, ng/L	13188	5779	–	5217	29686
Weight, kg	94	89	89	83	92

*Therapy started after admission in March 2006 with bevacizumab (5 mg/kg intravenously every 28 days), cyclophosphamide (1.000 mg total intravenously every 28 days) and dexamethasone (40 mg orally daily for 4 consecutive days every 15 days for 2 months). IL-6 indicates interleukin-6 (normal range < 3.3 ng/L); β2 MG: β2 microglobulin (<2.4 mg/L); VEGF: vascular endothelial growth factor (<50 pg/mL); pro-BNP: pro-brain natriuretic peptide (< 90 ng/L). *The first serum VEGF was measured five days after onset of immunochemotherapy.*

reduction of high VEGF-levels might lead to increased apoptosis of motor neurons and endothelial cells. Contrary to this experience, Badros and his co-workers presented a second case of successful bevacizumab treatment in a patient with POEMS syndrome.[2]

It has been suggested that neovascularization induced by up-regulation of proinflammatory cytokines plays an important role in the pathogenesis of POEMS syndrome.[5,6] Changing cytokine interactions by specific targeting may be a promising therapeutic option. However, the use of VEGF blockage as a causative treatment has its risks because the complex causes underlying this disease may be significantly worsened by the well-known adverse effects of this drug. One could speculate that symptoms like diarrhea and pulmonary hypertension might be due to regression of the normal capillary bed in different organs causing a vascular remodeling by reducing chronic high VEGF-levels, as reported by Voelkel *et al*.[7]

The initial improvement by our patient experienced confirms the value of bevacizumab in POEMS syndrome. But considering the subsequent clinical course, we support Straume's call for caution before using bevacizumab since the interactive role of VEGF in this disease remains unclear and further investigation is needed.

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