Letters to the Editor

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High-dose intravenous azathioprine pulse treatment in refractory Wegener’s granulomatosis

Sir, in Wegener’s granulomatosis (WG) standard therapy with cyclophosphamide (CYC) is limited by treatment-associated short- and long-term morbidity and mortality as well as insufficient response in about 10% of all cases [1]. Several therapeutic regimes have been used for refractory disease with varied results, including monoclonal antibodies to TNF-α [2] and different surface markers of T-cells (CD4, CD 52) [3] and B-cells (CD20) [4]. We report two patients with WG responding insufficiently to standard therapy, TNF blockade and rituximab in succession, but treated successfully with intravenous (i.v.) azathioprine (AZA). Both participants who were treated gave their informed consent. They fulfilled the Chapel Hill Consensus Conference definition [5] and the ACR criteria [6] for WG. Diagnosis was based on a typical clinical presentation and biopsy findings, supported by the presence of cANCA/PR3-ANCA. Sufficient activity of thiopurine methyltransferase (TPMT), an inactivating enzyme in the metabolism of AZA, was determined before treatment. AZA (1200 mg in 1000 ml NaCl 0.9% i.v., corresponding to 17 mg/kg body weight) was given over a 24-h period (50 ml/h) once monthly with antiemetic prophylaxis (ondansetron). Additive AZA was given orally (100 mg per day) in weeks 2 and 3 between each pulse, with regular monitoring of the white blood cell count. After completing six pulses, therapy was continued with daily AZA (100–150 mg/day) orally.

Patient 1, a 33-yr-old female with WG and predominantly ENT involvement, was started on CYC (1300 mg every 6 weeks i.v.) and prednisolone (PRD). Because of the development of an increasing retro-orbital mass after 9 months of CYC, therapy was intensified by adding infliximab (5 mg/kg body weight every 6 weeks). Continuing and wearing right-sided supraorbital pain with an increasing demand for PRD (60 mg/day) was attributed to massive progress of the retrobulbar granuloma. Thus, CYC and infliximab were stopped after 28 weeks of combined treatment and rituximab (375 mg/m²) was started in combination with MTX (20 mg/week i.v.) instead. In addition to further progress of the retro-orbital mass, a necrotizing and destructive inflammation of the right-sided lower eyelid soon appeared (Fig. 1). The decision was made to change treatment to i.v. azathioprine pulse therapy (1.2 g). After the first two i.v. applications, less pain and better vision were reported by the patient. Strong improvement continued up to the sixth AZA pulse, and regression of endonasal and orbital disease activity and a better motility of the right eye were documented during the next 12 months (Birmingham Vasculitis Activity Score (BVAS) 1:0, BVAS 2:0).

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Haematopoietic stem cell transplantation for refractory Takayasu’s arteritis

Sir, Takayasu’s arteritis is a rare large-vessel vasculitis with a variable natural history. Manifestations range from asymptomatic disease to catastrophic neurological impairment and 5-yr survival is 60–70% in up to 25% of patients with progressive disease. Fifty per cent of patients respond to steroids and 30–50% of non-responders benefit from other forms of immunosuppression [1].

Eleven cases of small- or medium-vessel vasculitis submitted to autologous haematopoietic stem cell transplantation (HSCT) have been reported worldwide [2, 3] and a further two in Brazil [4, 5]. Outcome is variable: 1/1 complete remission (CR) in polyarteritis nodosa, 1/3 CR in Wegener’s granulomatosis, 1/3 CR and 1/3 partial remission (PR) in Behçet’s disease, 2/3 CR in cryoglobulinemia and 1/1 PR in an undifferentiated vasculitis. To the best of our knowledge, this is the first case of HSCT for large-vessel arteritis reported in the literature; it was briefly presented at an international meeting [6].

Takayasu’s arteritis was diagnosed in June 1990 in a 41-yr-old Brazilian woman presenting with upper and lower limb claudication, dizziness, headache, polyarthralgia, malaise, myalgia and occasional fever. There was no kidney or heart involvement. Doppler ultrasound (US) showed biphasic or monophasic pulse waves with slow speed in the abdominal aorta (41 cm/s) and in the upper and lower limbs. The arteriography showed irregularities and stenosis of the abdominal aorta, of both carotid and iliac arteries and of the left subclavian artery. The patient was treated with various immunosuppressive agents, such as steroids (two pulses of 6-methylprednisolone 1 g x 3, and up to 80 mg prednisone per day since diagnosis), oral cyclophosphamide (50 mg/day for 30 days), mycophenolate mofetil (MMF; 2 g/day for 11 months), methotrexate (25 mg/week for 6 months) and chlorambucil (6 mg/day for 3 months), but none of those therapies stopped disease progression. In October 2002, while on MMF and steroids, a magnetic resonance angiogram (MRA) showed narrowing and irregularities in both carotid and subclavian arteries and in the brachiocephalic artery (Fig. 1A). This result was associated with worsening of clinical symptoms and prompted the patient and her physician to choose our experimental protocol of autologous HSCT for refractory autoimmune diseases [4, 5] which was approved by the Committee of Ethics in Research of the University Hospital of the School of Medicine of Ribeirão Preto. An informed consent according to the Declaration of Helsinki was signed. In December 2002 fibromyalgia was also diagnosed.

In March 2003 haematopoietic stem cells were mobilized from the bone marrow with cyclophosphamide (2 g/m²) and granulocyte colony-stimulating factor (G-CSF) (10 µg/kg/day), collected by leucapheresis (two sessions) and frozen in liquid N₂. In April 2003 the patient was conditioned with cyclophosphamide (50 mg/kg/day x 4) plus rabbit anti-thymocyte globulin (ATG; Tecelac, Biotest, Germany; 4.5 mg/kg divided in five doses and preceded by 125 mg of hydrocortisone), followed by stem cell infusion (3.9 x 10⁶/kg CD34+ cells). Complications during the neutropenic phase included fever of unknown origin, hyperglycaemia, subconjunctival haematomata and emotional liability. Cefepime and teicoplanin were used as empirical treatment for neutropenic fever, acyclovir for prophylaxis of herpes infection and trimethoprim/sulphamethoxazole for prophylaxis of Pneumocystis carinii infection. G-CSF (5 µg/kg/day) was used from day 5 through to neutrophil engraftment which was observed on day 9. On day 14 the patient presented with a skin rash and on day 16 she was discharged from the hospital. Amenorrhea developed in the pre-transplant period after use of leuproide and persisted after transplantation. The clinical condition improved rapidly; there was complete resolution of headache, dizziness and malaise while limb claudication was significantly reduced. After transplantation (day 320), arterial pulses of the left lower limbs and of the carotid arteries showed normal shape and speed by Doppler US and the wave speed of abdominal aorta increased to 73 cm/s. There were still stenotic areas in the arteries of the upper limbs and a low-speed biphasic pattern in the wave speed of the right lower limb. In the last clinical follow-up on day 270 the patient presented manifestations only of fibromyalgia and hand paraesthesia. C-reactive protein was 2.4 mg/dl pre-transplant and 0.8 mg/dl on day 147 and day 183. The erythrocyte sedimentation rate was 84 mm/1st h (Westergren method) pre-transplant, and 34 mm/1st h on day 350. Immunophenotyping of peripheral blood lymphocytes showed inversion of the CD4/CD8 ratio, and reduction of CD4 memory cells at day 210 post-transplantation. Pre- and post-transplantation immunoglobulin levels also showed a significant reduction.

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Fig. 1. Magnetic resonance angiography images before (A) and 60 days after (B) haematopoietic stem cell transplantation showing correction of the stenosis of the brachiocephalic artery (arrow 1) and reduction in the irregularities of the left carotid artery (arrow 2) and of the left subclavian artery (arrow 3).