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Case report

Successful autologous haematopoietic stem cell transplantation for refractory myasthenia gravis – a case report

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Abstract

Myasthenia gravis (MG) is an autoimmune disease, with immune reactivity against the post-synaptic endplate of the neuromuscular junction. Apart from symptomatic treatment with choline esterase blockers, many patients also require immunomodulatory treatment. Despite existing treatment options, some patients are treatment refractory. We describe a patient with severe MG refractory to corticosteroids, four oral immunosuppressants, cyclophosphamide, rituximab and bortezomib who was treated with autologous haematopoietic stem cell transplantation. Two years after this, the patient has significantly improved in objective tests and in quality of life and leads an active life. Diplopia is her only remaining symptom and she is completely free of medication for MG. We believe that autologous haematopoietic stem cell transplantation can be an effective therapeutic option for carefully selected cases of severe, treatment refractory MG.

Keywords: Myasthenia gravis; Autologous haematopoietic stem cell transplantation

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease, with immune reactivity against the post-synaptic endplate of the neuromuscular junction [1,2]. Apart from symptomatic treatment with choline esterase blockers, many patients also require immunomodulatory treatment. Despite existing treatment options, some patients are treatment refractory. High-dose cyclophosphamide has been tried in such patients [3,4]. In addition, allogenic haematopoietic stem cell transplantation has been reported in one patient [5] and recently a case series of seven patients treated with autologous haematopoietic stem cell transplantation (AHSCT) for MG was published [6]. We describe another patient with severe treatment refractory MG who was treated with AHSCT.

2. Case report

The patient is a woman who was diagnosed with MG at the age of 26 when she presented with diplopia, ptosis and limb weakness. Diagnostic workup revealed acetylcholine receptor (aAChR) autoantibodies, pathological decrement on repetitive nerve stimulation and a positive edrophonium test. Thymectomy by a suprasternal approach was performed at age 26. Due to remaining MG symptoms she underwent a transsternal thymectomy at age 36, with removal of remaining thymic tissue. On both occasions, thymic histology stated thymic hyperplasia with no signs of thymoma. Treatment with pyridostigmine was initiated at diagnosis and continued all throughout the years. For a long time, the patient's MG symptoms were reasonably well controlled with pyridostigmine, intermittently in combination with corticosteroids. She was able to work part time as a nurse and to give birth to and raise a child. During these years the severity of her MG varied between MGFA [7] class II and class III. Due to increasing weakness, azathioprine was initiated at the age of 52. Nevertheless, symptoms deteriorated over the years following and

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Table 1
Treatment for MG before AHSCT.

Drug	Dose	Administration	Effect
Pyridostigmine	360–840 mg/day	Age 27 to 64[1]	Moderately positive
Terbutaline	7.5–15 mg/day	Age 35 to 64[2]	No effect*
Methylprednisolone	3–4 g total dose	Three times, at age 38, 46 and 51	No effect
Azathioprine	150 mg/day	Eight months[3], age 51	No effect
Prednisolone	10–60 mg/day	Several times, for weeks to months	No effect
Sirolimus	2 mg/day	Two months[3], age 53	No effect
Rituximab	2 g total dose	Age 54	No effect
Cyclosporin	350 mg/day	Nine months[3], age 54	No effect
Mycofenolat mofetil	2 g/day	Ten months at age 57 and 12 months at age 61[3]	No effect
Bortezomib	25 mg total dose[4]	Age 59	No effect
Cyclophosphamide	10.6 g total dose	Age 61	No effect
IvIg	20–30 g	Numerous treatment series with 20–30 g × 1 × III-V and several periods of 20–30 g given every third or fourth week during the last 13 years before AHSCT.	Varying from none to good but short lasting.
Plasmapheresis	Usually three to five exchanges	Numerous treatment series during the last 13 years before AHSCT.	Varying from slightly positive to very good but short lasting.

[1] From diagnosis to half a year after AHSCT.
[2] Stopped two months after AHSCT.
[3] Withdrawn due to side effects.
[4] Given over a period of three months. A new cycle of bortezomib was started six months later and was stopped when the patient developed a myasthenic crisis during this new cycle.
* No objective improvement documented in medical records. The patient's own opinion is that terbutaline had a slightly positive effect.

the patient was treated with pyridostigmine, prednisolone, azathioprine, and intermittent intravenous immunoglobulin (IvIg) or plasmapheresis. When that treatment failed, she also received successive treatments with sirolimus, cyclosporin, cyclophosphamide, rituximab, mycophenolate mofetil and bortezomib. Neither standard treatment nor more advanced immunomodulatory treatment resulted in sustained improvement. The patient required hospitalization numerous times due to repeated MG crises, some of which involved respiratory insufficiency that necessitated assisted ventilation in an intensive care unit (ICU). During these years, her MG severity varied between MGFA class III and class V. An overview of the patient's medication for MG before AHSCT is given in Table 1. At the age of 63 the patient experienced only moderate and short-lasting relief from plasmapheresis, given in series of five treatments with only a few weeks in between series. Her dose of pyridostigmine was 120 mg five times per day and she also took prednisolone 10 mg per day. She had severe generalized myasthenia and reported very poor quality of life. Her MG composite (MGC) [8] score was 26. The aAChR level was 50.5 nmol/L. At this point AHSCT was suggested and discussed with the patient. The patient agreed to AHSCT, which was performed at the age of 64.

2.1. AHSCT procedure and haematological follow-up

Peripheral haematopoietic stem cells were mobilized with rituximab 375 mg/m^2 iv on day 0 and filgrastim 1.5 ME/kg sc, on days 1–4. Prednisone was given day 0 (Solu-Medrol 40 mg) and on days 1–4 (Prednisolone 25 mg). A leukapheresis for harvesting of the haematopoietic stem cells was performed on day 4. No ex vivo graft manipulation was performed. As conditioning treatment BEAM, carmustine 300 mg/ m^2 iv was given on day -7, on days -6 to -3 cytarabine 200 mg/m^2 iv daily and etoposide phosphate 200 mg/ m^2 iv daily, on day −2 melphalan 140 mg/m^2 iv, day −2 and −1 rATG 2,5 mg/kg/day. At day 0, 2.2×10^6/kg CD34+ cells was infused. Engraftment with ANC>0.5×10^9/L and no further need of platelets transfusion was achieved on day +11.

From the start of conditioning muscle weakness worsened and PEF decreased. Day-1 neutropenic fever developed and meropenem iv was started. No infectious focus was localized and rATG was thought to be the cause. On day −1 the patient was moved to the ICU and on day 0 severe hypercapnia rapidly developed and invasive ventilator treatment was started and continued until day +6. Plasmapheresis with immune absorption column was performed on day +5 and day +7. On day +6 a drug related exanthema developed. There were no signs of serum sickness. On day +11 the patient could leave the ICU and on day +19 she was discharged from the transplant unit and transferred to a neurology ward. Prophylaxis against fungal, viral and bacterial infection was administrated during neutropenia. Prophylaxis against varicella virus and pneumocystis jiroveci was continued for an additional three months.

At follow-up, blood counts were close to normal with a slight thrombocytopenia (platelets 144×10^9/L) and anaemia (haemoglobin 101 g/L), which were in line with the habitual level for the patient. No CMV or EBV reactivation was seen during the almost six months that this was monitored. We used flow cytometry analysis every six months to monitor the immune reconstitution. The number of T cells was never affected, as expected. The B cell count on the other hand was non-measurable six months post transplantation and almost