Bortezomib in severe MuSK-antibody positive myasthenia gravis: first clinical experience

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Background

Myasthenia gravis (MG) is an autoimmune disease caused by antibodies to different antigens of the neuromuscular junction, in particular to acetylcholine receptor (AChR) and muscle tyrosine kinase (MuSK).[1] Standard therapies comprise pyridostigmine, glucocorticosteroids, azathioprine or alternatively mycophenolate mofetil, cyclosporine A and tacrolimus. In severe MG, escalating immunotherapy by application of plasma exchange (PE), immunoadsorption (IA), intravenous immunoglobulins (IVIGs), rituximab or cyclophosphamide has to be initiated.[2] For those patients who do not respond to these strategies, novel therapeutic options are critically needed. Such 'cutting edge' treatments may be recruited from the therapeutic arsenal used in other autoimmune or neoplastic diseases (e.g. rituximab, an established compound in lymphoma therapy was recently transferred to MG therapy). The whole spectrum of upcoming and in part very specific and sophisticated new immunotherapies includes a variety of T-cell directed monoclonal antibodies that block the intracellular cascade associated with T-cell activation, monoclonal antibodies directed against key B-cell molecules, and inhibitors of complement, cytokines and transmigration molecules (reviewed by Dalakas[3]).

Based on experimental studies, the proteasome inhibitor bortezomib is suggestive to become another new therapeutic agent in MG.[4–6] Bortezomib is known to be very effective in the elimination of malignant plasma cells in multiple myeloma,[7] and in particular in the depletion of short-lived and long-lived B-cells.[8,9] Since in MG plasma cells are the main persistent players in antibody production, we selected bortezomib (Velcade®, Millenium Pharmaceuticals, Cambridge, Massachusetts, USA) for treatment in a patient with severe refractory MuSK-antibody positive MG.

The procedure was approved by the Ethics Committee of the Medical Faculty of the Ruhr-University of Bochum (No. 4856-13). The patient gave written informed consent for publication of the data in an international medical journal.

Case report

A 56-year-old woman developed double vision and Hashimoto thyroiditis 3 months before admission to our department. Within 2 months she developed severe dysphagia, dysarthria and proximal arm muscle weakness and was diagnosed with MuSK-antibody positive MG. She was treated with pyridostigmine (510 mg per day) and oral steroids (40 mg per day) in another hospital for 4 weeks. Due to deterioration of bulbar symptoms she was transferred to our intermediate care unit. Fiber endoscopy revealed a hypotonic and slowed swallowing act with penetration of food at the epiglottis. Due to risk of aspiration, the patient received a transient PEG fistula. Initial clinical examination revealed 29 points on the MG composite scale. Arm extension time was 92 s, leg extension time 39 s and head holding time 12 s (Besinger score 1.3). She received 20 g methylprednisolone, 270 mg pyridostigmine and 100 g IVIG within the first five days, but did not improve. Subsequently methylprednisolone was elevated to 30 mg per day and pyridostigmine to 440 mg daily. Three PE procedures and two IAs with insufficient response were performed during the second and third weeks of her stay, followed by rituximab 250 mg at the end of the fourth week. Again, intravenous immunoglobulins were reapplied at a dosage of

60 g during the fifth week. Due to the severity of the disease, in particular of the bulbar symptoms (see video 1) that necessitated a PEG fistula, we decided to further escalate immunotherapy. Nineteen days after rituximab therapy, bortezomib subcutaneously (s.c.) according to the standard scheme (bortezomib 1.3 mg/m^2 body surface s.c. four times within 2 weeks and protective co-medication with aciclovir 400 mg twice daily and cotrimoxazole 960 mg BID three times weekly for 2 months) was given. After the first injection of bortezomib there was some improvement of dysarthria and after the second injection progressive improvement of dysphagia, head holding and dysarthria could be observed, as demonstrated in video 2. CD19-positive cells were reduced to 0.5% (about 3.5/µl). After the third injection of bortezomib the patient showed transient diplopia and ptosis, but apart from this the Besinger score improved from 1.14 before bortezomib to 0.62 after the last injection of bortezomib. Speech and swallowing improved to almost normal, allowing for removing the PEG fistula. Double vision still occurred after 11 s when looking to the left side, but ptosis had resolved completely. Her arm extension time improved to 172 s, leg extension time to 67 s and head holding time to 40 s, reflected by only two points on the MG composite scale. MuSK-antibody titer declined from over 12 U/ml to 1.76 U/ml (normal below 0.4 U/ml). Pyridostigmine therapy was continued at 180 mg/day. The patient was dismissed after 2 weeks. After 3 months her CD19 cells were still depleted with 46 cells/µl. She stayed in pharmacological remission for 6 months. In contrast to other MuSK patients, she profited from low-dose pyridostigmine.

Due to mild deterioration after 6 months and increase of CD19 cells to 177/µl, as well as of MuSK antibodies to 7.24 U/ml, oral steroids were reintroduced at 60 mg for 3 days, and then 40 mg and 20 mg for 3 days each, and the patient was treated with rituximab 500 mg again. The patient is stable since then under 5 mg methylprednisolone and pyridostigmine 180 mg per day.

Discussion

In our study we report a female, de-novo MuSK-antibody positive MG patient with a severe disease course. In the acute phase she was non-responsive to high-dose IVIG, combined PE and IA treatment, steroids intravenously and orally and intravenous rituximab, fulfilling criteria for refractory MG.[10] Significant and rapid improvement of her severe myasthenic symptoms could be achieved by treatment with s.c. bortezomib within a quite short period of time. We hypothesize that probably long-lived plasma cells non-responsive to antiproliferative immunosuppressive drugs and resistant to B-cell depleting therapies via anti-CD20 may be the main target. The high metabolism of antibody-secreting plasma cells renders them highly susceptible to proteasome blockade.[11] Unfortunately there is no direct laboratory test available to verify the elimination of such plasma cells, which may reside at low frequency in, for example, bone marrow.

Bortezomib is capable not only of depleting short-lived and long-lived plasma cells by aberrant degradation of defective ribosomal proteins in the endoplasmic reticulum or by inducing apoptosis, but inhibits also the antiapoptotic nuclear factor κB signaling pathway. It suppresses the release of proinflammatory cytokines, reduces type I-IFN activity in rheumatoid arthritis and depletes alloreactive T-cells.[9] However, it is unclear which effect is most likely to explain the quite rapid improvement we could observe in our MuSK-antibody positive MG patient. We hypothesize that this effect may far more be related to prolonged survival of attacked endplate structures by proteasome inhibition than to the effects on long-lived B-cells.

Strikingly positive therapeutic effects of bortezomib have been shown also in refractory thrombotic thrombocytopenic purpura[12] and systemic lupus erythematosus[13] with intravenous administration of bortezomib and also with s.c. bortezomib administration in multiple myeloma[6] and in pediatric autoimmunity,[14] as well as in a single ANCA patient.[15] In an experimental rat model for MG it could be shown that bortezomib leads to reduced acetylcholine receptor-antibody secretion, prevention of motor endplate damage and clinical improvement.[4] In addition, specific effects of bortezomib on plasma cells in cultured thymic cells from nine early-onset MG patients have been reported.[6]

With regard to the development of polyneuropathies, s.c. application of bortezomib seems to be better tolerated than intravenous application.[7] A relevant side effect of bortezomib in oncological diseases are neuropathic symptoms,[16] since neuronal cells may also suffer from

metabolic disturbances caused by bortezomib, in particular when repeated cycles within 4 weeks are given in lymphoma patients. In contrast, we administered only a single cycle with four s.c. injections at 1.3 mg/m^2 body surface, and up to now did not observe any disturbance of the peripheral nervous system.

Thus, bortezomib seems to be a potent agent to inhibit plasma cell activity and thereby antibody production in severe refractory MuSK-antibody MG. In combination with rituximab, the therapeutic effect seems to be strong enough to achieve long-term stabilization of MG. The co-administration of rituximab may have synergistic effects due to the depletion of different CD19 cell subsets. This may help to avoid side effects such as polyneuropathy, which may occur due to frequent administration of bortezomib.[16] We conclude that the introduction of bortezomib therapy was essential to stabilize the disease in our patient.

Of course, further controlled studies of bortezomib in severe MG are warranted.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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