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Case Report

Breakthrough treatment with bortezomib for a patient with anti-NMDAR encephalitis

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ABSTRACT

After its discovery, anti-*N*-methyl-D-aspartate receptor encephalitis is now an established neuroinflammatory disorder, for which various immune-suppressive strategies have been successfully proposed. The most commonly applied therapy includes high dose cortico-steroids, as well as plasma exchange procedures (PLEX), and subsequently either oral immunosuppressants, such as azathioprine or B-cell depletion by the anti- CD20 monoclonal antibody rituximab.

However, in rare cases we are faced with patients who do not respond to either oral immunosuppressants, or rituximab. Hence, we have recently described bortezomib, a proteasome inhibitor as a potentially effective treatment in patients not responding to first-line immune-therapies. Particularly, plasma cells as mature, non-dividing antibody secreting cells are highly sensitive to proteasome inhibitors. Here, we report of a patient with severe, and prolonged anti-NMDAR encephalitis despite PLEX and repeatedly applied high dose rituximab. As documented in the accompanying video that shows the different stages before, and immediately after bortezomib therapy the patient recovered swiftly.

1. Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is a rare, and severe auto-immune mediated encephalitis presenting with psychiatric symptoms, seizures, autonomic instability and dyskinesia [1]. In some cases, it affects young woman with ovarian teratomas, but is also observed on autoimmune grounds in both sexes [1].

NMDAR-antibodies are usually found in serum und cerebrospinal fluid. Additionally, most patients have intrathecal synthesis of antibodies. Due to the auto-antibody mediated immune-pathogenesis, therapies targeting the humoral immunity have been effective, i.e. plasma exchange procedures (PLEX or IA) and subsequent B-cell depletion, i.e. with rituximab. However, a subgroup of the patients have been shown to be non- responsive to B-cell depletion. Hence, we have recently described bortezomib, a proteasome inhibitor as a potentially effective treatment in patients not responding to rituximab [2]. Plasma cells as mature, non-dividing antibody secreting cells are resilient towards B cell depleting antibodies, and survive in their niches, however have been shown to be highly sensitive to proteasome inhibitors [3]. It might be an explanation that proteasome inhibitors prevent immigration of novel autoreactive B cells, plasma cells and antibodies into the brain.

Here, we report of a patient with severe, and prolonged anti-NMDAR encephalitis despite PLEX and high dosages of anti-CD20 antibody rituximab who recovered within a short time after bortezomib injections as shown in the accompanying video documentation.

2. Case report

A 22-year-old woman presented with a subacute psychosis including visual hallucinations at the emergency department of a hospital in Luxembourg in September 2016. She had developed prodromal signs with severe anorexia the weeks before. Neurological testing revealed no paresis, sensory deficit, or meningism. Cranial MRI was normal. A lumbal puncture showed 65 lymphocytes per uL. Based on these findings antibiotic and antiviral therapy including ceftriaxone, aciclovir and methylprednisolone was initiated. During follow-up, bacteriological and virological testing of the CSF showed negative results for HSV,

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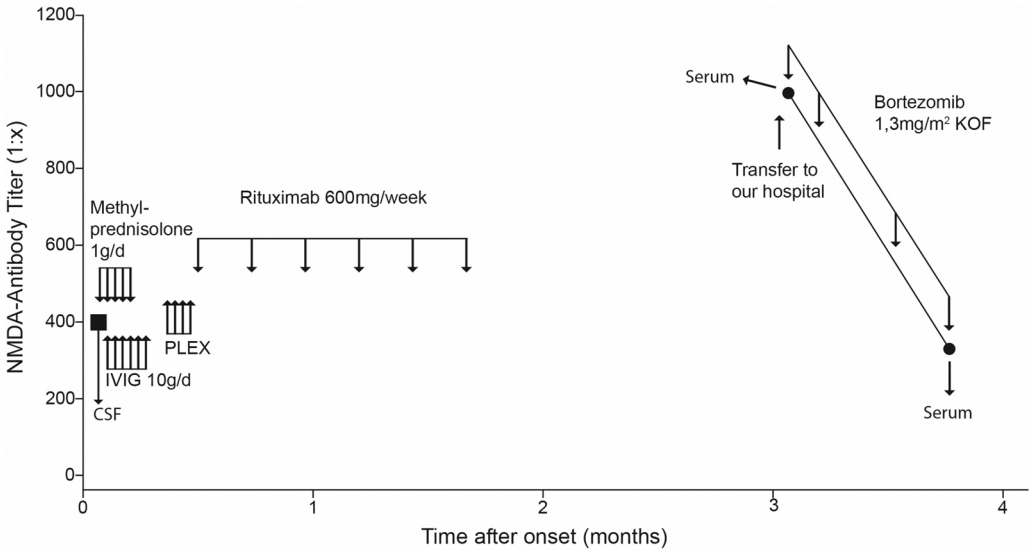

Fig. 1. Clinical Course and Treatment. The x-axis indicates the number of months after disease onset. The y-axis indicates the anti-*N*-methyl-D-aspertate receptor antibody titer measured by a standard cell-based assy in the cerebrospinal fluid (CSF) and serum. IVIG indicates intravenous immunoglobulins and PLEX plasma exchange.

Neisseria, haemophilus, Streptococcus, and E. coli. Additionally, serum blood test showed negative results for listeria and brucellosis. Due to blurred consciousness the patient was sedated and intubated after admission to the ICU. After occurrence of generalized epileptic seizures the patient was treated with levetiracetam and midazolam. In the further course quadruple combination of epileptic treatment was established to achieve freedom of seizures (daily: levetiracetame 2 g, topiramate 175 mg, lacosamide 200 mg, and valproate 300 mg).

Paraneoplastic antibody panel testing revealed the presence of anti-NMDAR antibodies in the CSF (1:400). Treatment was started with high dose i.v. methylprednisolone (cumulative 5 g for 5 days), 60 g intravenous immunglobulines for 6 days and four cycles of PLEX. Hereafter, rituximab with a cumulative dose of 3.6 g was initiated (600 mg once a week) over the course of following weeks (Fig. 1). A second MRI (performed before therapy with rituximab) showed hyperintense signals in the vermis, nodulus, and both cerebellar hemispheres in fluid-attenuated inversion recovery (FLAIR) and T2-weighted MRI. Recently performed MRI showed no new lesions.

Two months after onset, due to continuous deteriorated state of the patient, she was transferred to our neurological department. At that time, the patient presented with stuporous phases and did not respond adequately. Speech production was poor, and she was mostly bedridden. Infrequent stereotypies with fiddling movements were observed (see video 1 day '*before starting bortezomib*'). CD19+ B-cells were completely depleted and serum NMDA-R antibody titer was 1:1000. Owing to her severe and treatment-refractory deficits she was treated with bortezomib using the standard oncologic regimen after obtaining informed consent from her guardian: four subcutaneous injections of 1.3 mg/m [2] on days 1, 4, 14 and 25; comedication with 400 mg aciclovir sodium twice a day and 960 mg of cotrimoxazole 3 times a week for 3 months. Due to neutropenia (minimum level 410/µl) that occurred shortly after the second injection, G-CSF support was necessary. Blood counts recovered soon after.

During the therapy with bortezomib, a fast improvement of neurological deficits was visible as shown by video documentation (see day 1 after first injection). The infrequent stereotypies with fiddling movements were reduced subsequently. After 2 weeks assisted walking was possible and speech production improved. NMDA-R antibody titer after four bortezomib injections was tested at 1:320. She was then transferred to extensive rehabilitation in her homecountry Luxembourg.

3. Discussion

We describe a patient with a severe course of anti-NMDAR encephaltitis without immediate response to first-line treatment regimen with corticosteroids, PLEX, and rituximab. Prior case reports showed a distinctly beneficial effect in combination of rituximab and the proteasome inhibitor bortezomib [2,4]. Although a delayed effect of previous treatment cannot be ruled out entirely, the immediate improvement beginning after first injection of bortezomib as shown in the video documentation is suggestive for a specific effect of bortezomib. Particularly in this case with a refractory auto-antibody mediated autoimmune disease we think, that the antibody response is mediated by long-lived plasma cells. These cells are extremely refractory to conventional immunosuppressive drugs such as B cell depletion regimens [5]. However, long-lived plasma cells can be targeted by proteasome inhibitors such as bortezomib [5].

4. Conclusion

The case presented here in addition to previously reported cases underline the potential therapeutic use of bortezomib as second-line agent in patients with anti-NMDA-R encephalitis who do not respond to B-cell depleting therapies.

Author contributions

Christoph Schroeder: Data collection, treatment, drafting, and revising the
manuscript.
Claude Back: Data collection, treatment, critical comments during manuscript Revision.
Ümmügülsüm Koc: Data collection, treatment
Katrin Strassburger-Krogias: Data collection, treatment
Anke Reinacher-Schick: treatment, Critical comments during manuscript
Revision.
Ralf Gold: Data collection, treatment, drafting and revising the manuscript,
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Aiden Haghikia: Data collection, treatment, drafting and revising the
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A. Reinacher-Schick received speaker's fees from Amgen, Roche, Pfizer, Sanofi-Aventis, Merck-Serono, Celgene, Shire, and has served as advisory board member for Amgen, Celgene, Merck-Serono, Pfizer, Roche, Sanofi-Aventis, Servier, Shire and receives search support from Roche, Sanofi-Aventis and Celgene.

R. Gold serves on scientific advisory boards for Teva Pharm. Ind. Ltd., Biogen Idec, Bayer Schering Pharma, and Novartis; has received speaker honoraria from Biogen Idec, Teva Pharmaceutical Industries Ltd., Bayer Schering Pharma, and Novartis; serves as editor for Therapeutic Advances in Neurological Diseases and on the editorial boards of Experimental Neurology and the Journal of Neuroimmunology; and receives research support from Teva Pharmaceutical Industries Ltd., Biogen Idec, Bayer Schering Pharma, Merck Serono, and Novartis.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2018.06.005.

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