

RESEARCH ARTICLE

Bortezomib treatment for severe refractory anti-NMDA receptor encephalitis

Yong-Won Shin^{1,2}, Soon-Tae Lee¹, Tae-Joon Kim¹, Jin-Sun Jun³ & Kon Chu¹¹Department of Neurology, Seoul National University Hospital, Seoul, South Korea²Yeongjusi Health Center, Gyeongsangbuk-do, South Korea³Department of Neurology, Kyungpook National University Chilgok Hospital, Daegu, South Korea

Correspondence

Soon-Tae Lee, Department of Neurology, Seoul National University Hospital, Integrated Cancer Care Center, Seoul National University Cancer Hospital, 101, Daehangno, Jongno-gu, Seoul 110-744, South Korea.
Tel: +82-2-2072-4757;
Fax: +82-2-2072-7424; E-mail: slee@snuh.org

Funding Information

This study was supported by the National Research Foundation of Korea (NRF) grants funded by the Ministry of Science, ICT & Future Planning, Korea (2016R1C1B2011815 and 2016M3C7A1914002 by Brain Research Program). Y-W.S. and S-T.L. were supported by the Lee Sueng Moon research fund of Seoul National University Hospital (3020170130).

Received: 20 December 2017; Revised: 23 February 2018; Accepted: 24 February 2018

Annals of Clinical and Translational Neurology 2018; 5(5): 598–605

doi: 10.1002/acn3.557

Introduction

Although most patients with autoimmune encephalitis respond to immunotherapy,^{1–3} a small, but significant, number of patients show an insufficient response even after aggressive immunotherapy; therefore, several treatment options are being explored.^{4–6} Long-lived plasma cells that can survive without cell division and continuously secrete autoantibodies are considered to contribute to the poor clinical course in the patients, given their known resistance to B-cell depleting agents, conventional immunosuppressants, and antiproliferative agents.⁷

Bortezomib is a proteasome inhibitor particularly effective against immunoglobulin-producing plasma cells, and

Abstract

Objective: To evaluate the therapeutic potential of bortezomib, a proteasome inhibitor that target plasma cells, in order to revive stalled recovery in patients with anti-N-methyl-D-aspartate (NMDA) receptor encephalitis who remain bedridden even after aggressive immunotherapy. **Methods:** We consecutively enrolled patients with anti-NMDA receptor encephalitis who remained bedridden after first-line immunotherapy (steroids and intravenous immunoglobulin), second-line immunotherapy (rituximab), and tocilizumab treatment, and treated them with subcutaneous bortezomib. Clinical response, functional recovery, and changes in antibody titer in the serum and cerebrospinal fluid were measured. **Results:** Before the bortezomib treatment, the five patients with severe refractory anti-NMDA receptor encephalitis were in a vegetative state. During the 8 months of follow-up period, three patients improved to minimally conscious states within 2 months of bortezomib treatment, one failed to improve from a vegetative state. However, no patient achieved functional recovery as measured by the modified Rankin Scale score (mRS). Three patients advanced to a cyclophosphamide with bortezomib and dexamethasone regimen, which only resulted in additional adverse events, without mRS improvement. Among the four patients whose antibody titer was followed, two demonstrated a twofold decrease in the antibody titer in serum and/or cerebrospinal fluid after 2 cycles of bortezomib. **Interpretation:** Although there were some improvements in severe refractory patients, clinical response to bortezomib was limited and not clearly distinguishable from the natural course of the disease. The clinical benefit of bortezomib in recent studies requires further validation in different clinical settings.

originally approved for the treatment of multiple myeloma.⁸ With the expectation of reviving stalled recovery by directly targeting plasma cells, bortezomib has been used to treat a few cases of refractory anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis.^{9–12} However, without consensus-driven treatment guidelines,¹³ these patients received heterogeneous pretreatment under different strategies. Bortezomib was introduced at variable points during the clinical course of disease and refractoriness was only leniently defined in some cases. In addition, case reports have an inherent tendency toward the publication of favorable results.

Given the unclear evidence to support the effect of bortezomib, we consecutively enrolled patients who remain

unconscious and bedridden after treatment with immunotherapeutic agents beyond second-line agents. We then assessed the efficacy and safety of bortezomib therapy in order to re-evaluate its therapeutic potential.

Methods

Study subjects

Among patients who were diagnosed and treated for autoimmune encephalitis in Seoul National University between 28 February 2017 and 9 September 2017, we consecutively enrolled all patients with anti-NMDAR encephalitis who (1) received first-line immunotherapy (steroids and intravenous immunoglobulin [IVIg] with or without plasmapheresis), second-line immunotherapy (rituximab with or without cyclophosphamide), and tocilizumab treatment; (2) remained bedridden due to unconsciousness and other symptoms for at least 3 months after the initiation of tocilizumab treatment; and (3) had demonstrated no prior improvement in the modified Rankin Scale (mRS) score, and relapsed (defined here as severe refractory patients). For comparison with historical controls, we reviewed the outcomes of patients with anti-NMDAR encephalitis who had remained bedridden and unconscious 3 months after initiation of rituximab therapy in our institution since May 2012. The use of bortezomib in anti-NMDAR encephalitis was approved by the institutional review board of Seoul National University Hospital. The need for obtaining informed consent from patients was waived by the same committee.

Diagnosis of anti-NMDAR encephalitis

Autoimmune encephalitis was diagnosed based on the clinical features of autoimmune encephalitis, a series of tests, including brain magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, electroencephalography (EEG), and tumor screening, as well as detection of the corresponding autoantibodies in the serum or CSF.¹⁴ A commercial indirect fluorescence assay (Euroimmun AG, Lübeck, Germany) was used to screen for antibodies to the NMDAR, leucine-rich glioma inactivated-1, contactin-associated protein-like 2, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) 1, AMPA2, and γ -aminobutyric-acid type B, as previously described.⁵ Classic paraneoplastic autoantibodies, such as anti-Hu, -Yo, -Ri, -CV2, -Ma2, -amphiphysin, -recoverin, -SOX1, and -titin were also screened using the immunoblotting method (Euroimmun). Anti-glutamic acid decarboxylase (GAD) antibody levels were measured by radioimmunoassay (RSR Limited, Cardiff, UK), as previously described.¹⁵ Possible infectious etiologies were excluded according to a protocol

previously described.⁵ Diagnosis of anti-NMDAR encephalitis was made according to the expert consensus criteria.¹⁶ All patients fulfilled criteria for probable anti-NMDAR encephalitis and a definite diagnosis was confirmed by the detection of anti-NMDAR antibodies in serum and CSF.

Treatment and evaluation of response to bortezomib

Patients were initially treated with 400 mg/kg IVIg for 5 days, in combination with 1000 mg intravenous (IV) methylprednisolone for 5 days. Rituximab treatment (375 mg/m² weekly for 4 weeks) was administered to all, and tocilizumab treatment (4–8 mg/kg monthly, IV) was initiated after rituximab in all patients. All patients maintained IVIg and rituximab therapy on a monthly basis, with the same daily dosage throughout the remaining treatment course, unless contraindicating medical conditions were present. Additional treatments with plasmapheresis (≥ 5 sessions per cycle), cyclophosphamide (750 mg/m² monthly, IV, for 3–4 months), and low-dose interleukin-2 (1 million units/day for 5 days, followed by repeated doses at 2-weekly to 1-monthly intervals) were variably instituted as determined by the attending physician. Bortezomib was administered for severe refractory patients. One cycle of bortezomib treatment consisted of a 3-week schedule. Subcutaneous injection (sc) of 1.3 mg/m² bortezomib with 20 mg IV dexamethasone, twice weekly for 2 weeks (days 1, 4, 8, and 11), was followed by a 10-day rest. All patients received prophylaxis with daily valaciclovir and trimethoprim-sulfamethoxazole during the bortezomib treatment. Two of the patients who showed limited response to bortezomib advanced to a CyBorD regimen, which consisted of weekly 300 mg/m² IV cyclophosphamide, 1.5 mg/m² sc bortezomib, and 40 mg IV dexamethasone. Four-weekly CyBorD treatments were counted as 1 cycle. A regimen that consisted of once-weekly administration of 1.5 mg/m² bortezomib with 20 mg dexamethasone was tried in one patient, because of cyclophosphamide-induced cytopenia, and because recent reports had shown that once-weekly bortezomib had similar efficacy with reduced adverse events.^{17,18}

Clinical improvement was determined by the treating physician, and the clinical global impression (CGI)¹⁹ was used as a summary measure for severity (CGI-S) and improvement (CGI-I). The CGI-S score ranged from 1 to 7: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients. CGI-I is rated on the following 7-point scale: 1 = very much improved since the initiation of treatment; 2 = much

improved; 3 = minimally improved; 4 = no change from baseline (the initiation of treatment); 5 = minimally worse; 6 = much worse; 7 = very much worse since the initiation of treatment. Functional recovery was evaluated using the mRS.

The anti-NMDAR antibody titer in the serum and CSF was checked at initial admission, before and after 2 cycles of bortezomib with serial dilution of samples. The last dilution that showed visible reactivity was defined as the titer. Adverse events were classified according to the Common Terminology Criteria for Adverse-Events v. 4.03.²⁰

Results

Clinical characteristics of severe refractory anti-NMDAR encephalitis

We enrolled five patients with anti-NMDAR encephalitis who met the criteria for severe refractory encephalitis. The clinical characteristics of these patients are summarized in Table 1. When initiating the bortezomib therapy, patients had been under treatment for a median of 5 months (3–12 months), and had received 4–6 immunotherapeutic agents (Table 1 and Fig. 1). Plasmapheresis was performed for two patients, and cyclophosphamide and low-dose interleukin-2 were administered for one patient, in addition to our routine treatment (methylprednisolone, IVIg, rituximab, and tocilizumab). Ovarian teratomas were identified and surgically removed for all female patients. All patients received tocilizumab after second-line immunotherapy for at least three cycles (median [range], 4 [3–8] cycles). According to our previous report, patients who responded to tocilizumab showed mRS improvement within 1–2 months (cycles) after tocilizumab therapy.⁵ However, all the patients remained vegetative and demonstrated the accompanying movement symptoms, including oromandibular dyskinesia, stereotypic limb movements, rigidity, and/or abnormal posture. Patients 1–4 underwent a tracheostomy and the tracheostomy tubes were maintained because of unstable respiration, decreased consciousness, hypersalivation, or recurrent pneumonia. EEG showed nearly continuously generalized slow wave activity for all patients, in accordance with diffuse cerebral dysfunction.

Treatment effect of bortezomib on the severe refractory anti-NMDAR encephalitis

The median (range) period from disease onset to initiation of immunotherapy was 11 (7–70) days, and to administration of bortezomib was 5 (5–12) months. There was a median interval of 3 (2–10) months from the

administration of tocilizumab to that of bortezomib. Three patients showed improvement in consciousness level. Signs of a minimally conscious state were noticed after 1–2 cycles of bortezomib (after 4 weekly bortezomib treatments for patient 5). All patients showed a decrease in their movement symptoms, and patients with central hypoventilation and other autonomic dysfunction also showed a degree of improvement. The CSF antibody titer was reduced by a single dilution (1/2) in half of the patients who underwent follow-up evaluations. The serum antibody titer changes varied within a single dilution among patients (Table S1). The CyBorD regimen was initially planned for patient 5; however, the patient developed anemia and neutropenia after the first cycle, and recurrence of neutropenia after the second administration of CyBorD. The patient was therefore maintained on once-weekly bortezomib treatment and experienced no further adverse events. The degree of improvement in patient 5 under once-weekly bortezomib treatment regimen was similar to that of other patients during the 2-month follow-up period.

During the 8-month follow-up of four of the patients, three patients showed further improvements in consciousness. Two of these could recognize and respond to their caregiver, follow simple commands, and verbalize simple words, and showed emotional responses such as smiling and frowning. The other patient improved to a minimally conscious state and showed some reduction in the frequency of movement symptoms. Patient 4 showed a further reduction in stereotypic movements and rigidity without obvious signs of a minimally conscious state. However, at the last follow-up, all the patients were still bedridden and required constant nursing care and attention (mRS score of 5), including two patients who advanced to a CyBorD regimen after 2–2.5 cycles of bortezomib. Treatment and clinical responses are summarized in Table S1 and Figure 1.

Comparison with a historical control group

Historical controls who showed a similar degree of severity and who remained refractory to 3 months of rituximab treatment were analyzed for comparison with the current bortezomib population. There were two female and one male patients; we excluded one male patient who was 66-years-old and refused further treatment, and was thus lost to follow-up after demonstrating refractoriness to rituximab therapy (Table S2). The three included patients had been followed up for 18–27 months and the two female patients underwent ovarian teratoma removal. All of them were comatose after rituximab therapy. Two patients used tocilizumab and showed no improvement in consciousness 3 months after initiation of tocilizumab.

Table 1. Clinical characteristics and treatment history of patients with severe refractory anti-NMDAR encephalitis.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	20	28	58	17	51
Sex	F	F	M	F	M
Presenting symptoms	Psy, Sp, Mm, Sz, Mv, C, A, HV Pleocytosis (1677/ μ L), elevated protein (49.8 mg/dL)	Psy, Sp, Sz, Mv, C, A, HV Elevated protein (66 mg/dL)	Psy, Sp, Sz, Mv, C, A Pleocytosis (98/ μ L), elevated protein (105 mg/dL)	Psy, Sp, Sz, Mv, C, A, HV Pleocytosis (27/ μ L)	Psy, Sp, Sz, Mv, C, A Pleocytosis (6/ μ L), elevated protein (48.1 mg/dL)
Brain MRI	Diffuse leptomeningeal enhancement	Increased T2 signal of bilateral hippocampus	Normal	Increased T2 signal of bilateral hippocampus	Mild white matter change in both cerebral hemispheres
EEG	Generalized delta slowing, multifocal spikes	Generalized delta slowing, delta brush	Generalized theta to delta slowing, delta brush	Generalized delta slowing	Generalized delta slowing
Tumor	Ovarian teratoma	Ovarian teratoma	None	Ovarian teratoma	None
Duration of disease onset to initiation of first-line immunotherapy (days)	15	7	70	11	9
First-line agents before bortezomib	MP, IVIg, PLEX (6 sessions)	MP, IVIg	MP, IVIg	MP, IVIg	MP, IVIg, PLEX (5 sessions)
Duration of disease onset to initiation of second-line immunotherapy (days)	43	23	75	14	29
Second-line agents before bortezomib	RTX	RTX, CYC (3 cycles)	RTX	RTX	RTX
Duration of disease onset to initiation of tocilizumab (days)	75	57	84	22	56
Number of cycles of TCZ before bortezomib	4	8	3	5	3
Other treatment before bortezomib therapy		IL2 (1 cycle)			

NMDAR, N-Methyl-D-aspartate receptor; Psy, psychiatric symptoms; Sp, speech dysfunction; Mm, memory dysfunction; Sz, seizures; Mv, movement disorder; C, consciousness decrement; A, autonomic dysfunction; HV, central hypoventilation; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; EEG, electroencephalography; MP, methylprednisolone; IVIg, intravenous immunoglobulin; PLEX, plasmapheresis; RTX, rituximab; CYC, cyclophosphamide; TCZ, tocilizumab; IL2, low-dose interleukin-2.

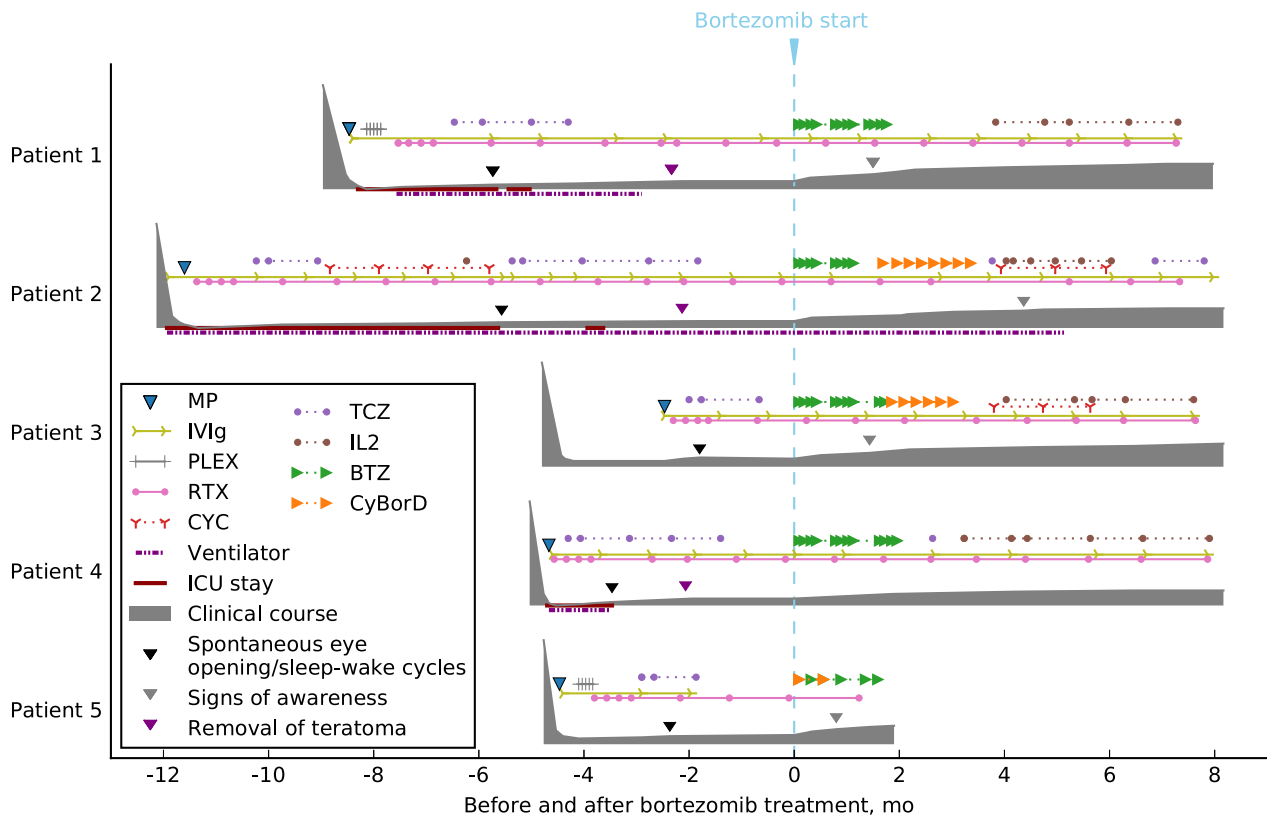


Figure 1. Treatment history and clinical course of patients with severe refractory anti-NMDAR encephalitis. All of the immunologic agents used during the treatment course of the five patients are presented schematically. Neurological deterioration and recovery are represented in the shaded area by an arbitrary scale, considering the level of consciousness, severity of accompanying movement disorders, frequency of seizures or cessation of status epilepticus, autonomic instability, and central hypoventilation. NMDAR, *N*-Methyl-D-aspartate receptor; MP, methylprednisolone; IVIg, intravenous immunoglobulin; PLEX, plasmapheresis; RTX, rituximab; CYC, cyclophosphamide; TCZ, tocilizumab; IL2, low-dose interleukin-2; BTZ, bortezomib; CyBorD, cyclophosphamide with bortezomib and dexamethasone regimen; ICU, intensive care unit.

One year after the onset, two of the three patients showed a slight improvement in consciousness level, without improvement in the mRS score, while one achieved an improvement in the mRS score (a score of 3). At 18 months, one patient improved to a minimally conscious state, one improved to an mRS score of 4, and the other further improved to an mRS score of 2. None of the study participants achieved an mRS score of more than 5 at 7–20 months (median 13 months) after the onset. Therefore, the introduction of bortezomib in the treatment course result in no meaningful change in the 1–1.5-year outcome compared with the other historic controls.

Safety profile

Four patients experienced adverse events of grade 3 and higher during the bortezomib therapy (Table S1), including pneumonia (grade 3, $n = 2$), neutropenia (grade 4, $n = 1$), febrile neutropenia (grade 3, $n = 2$), and anemia

(grade 4, $n = 1$). Other adverse events included anemia (grade 1–2, $n = 4$), neutropenia (grade 1, $n = 1$), leukopenia (grade 2, $n = 1$), ileus (grade 2, $n = 1$), and diarrhea (grade 2, $n = 1$). Three of the patients with severe adverse events suffered these events during CyBorD treatment. Adverse events during the bortezomib therapy without cyclophosphamide were usually not severe, were transient, and did not result in discontinuation of the treatment. Overall, adverse events were well managed for all patients and were acceptable, given the disease severity.

Discussion

In this study, all patients showed at least a minimal improvement in clinical symptoms after bortezomib treatment with manageable safety profile. However, there was no improvement in global mRS outcome in all patients for up to 8 months. The improvements in our study population were generally no better than those in a historical

control group with similar severity and duration of illness. Escalation to a CyBorD regimen was also not effective in improving mRS scores. Decrease in the serum and CSF antibody titers of more than twofold, considered as a substantial change,²¹ were not achieved after 2 cycles of bortezomib in any of the patients.

Bortezomib has demonstrated promising results in refractory cases of antibody-mediated autoimmune disorders, such as systemic lupus erythematosus,²² Sjögren syndrome,²³ acquired thrombotic thrombocytopenic purpura,²⁴ and in neurological disorders, such as neuromyelitis optica spectrum disorder²⁵ and muscle-specific tyrosine-kinase-antibody-positive myasthenia gravis.²⁶ Previous reports^{10,11} have suggested that bortezomib effectively targets plasma cells that produce anti-NMDAR antibodies. Other anti-inflammatory and immunomodulatory effects of bortezomib, such as inhibition of the nuclear factor- κ B signaling pathway, suppression of pro-inflammatory cytokines, induction of apoptosis of activated and proliferating T cells, and a shifted equilibrium of T cells from Th17 subsets to regulatory T cells,²⁷ may additionally contribute to clinical improvement.

However, the decrease in the antibody titers in the serum and CSF was not robust in our patients, or in previously reported cases.^{10,11} Furthermore, neurological and functional recovery in severe refractory patients was limited and all maintained an mRS score of 5 after treatment. The outcome of this study was quite different from that of previous reports, probably due to different clinical settings. In the largest case series by Scheibe *et al.*,¹¹ four of five patients had a severe clinical status at the initiation of bortezomib treatment. Three of these patients who showed marked improvement had a relatively low CSF antibody titer, started to show clinical improvement before bortezomib, or underwent early active treatment with bortezomib immediately after completing the rituximab treatment schedule. Only one patient who did not improve considerably showed findings similar to those in our cases. In another case report of two patients, by Behrendt *et al.*,¹⁰ CSF antibody titers were also low for both patients and one patient first showed clinical recovery with plasmapheresis monotherapy before relapsing. Therefore, most of the previous cases did not show the same degree of refractoriness to immunotherapeutic agents, CSF antibody titer, or clinical course and neurological severity as our cases.

There may be several explanations for the limited clinical responses in our patients. First, known intrathecal synthesis of anti-NMDAR antibody, pathologically confirmed by observing infiltration of antibody-secreting cells in the CNS,²⁸ indicate that plasma cells that translocate into the CNS space can evade attack from bortezomib, which had poor blood–brain barrier penetrance.²⁹ Most

specifically, long-lived plasma cells that can survive several months to years⁷ may continuously secrete autoantibodies in the CNS. The mechanism of the clinical response demonstrated in recent studies^{10,11} was also questioned in this regard by Rüegg and Irani.³⁰ Second, bortezomib is a reversible inhibitor,⁸ and the effect may not persist long enough to ameliorate the disease activity. Combination therapy with other agents is considered to be beneficial in this regard; however, the CyBorD regimen also failed to elicit improvement in mRS scores in our patients. Third, pharmacoresistance to bortezomib should be considered, but the probability of resistance to bortezomib in all patients who were also resistant to rituximab, tocilizumab, and cyclophosphamide is not high. Fourth, a lack of recuperative ability of these patients could be considered. We often try low-dose interleukin-2 treatment for refractory patients to selectively expand regulatory T cells and aid suppression of autoreactive T cells.⁶ However, there may be other factors reducing recuperative power. Non-immunotherapeutic approaches, such as ephrin-B2 administration,³¹ might aid recovery in the future.

This study was small, but involved consecutive patients, and is the largest case series involving severe refractory anti-NMDAR encephalitis within a fairly homogeneous pretreatment setting to date. Treatment responses were evaluated by the same physician who is experienced in current treatment strategies including tocilizumab, and who could determine the difference obtained by addition of bortezomib. Therapeutic intervention targeting B cells and plasmablasts by two different agents, rituximab and tocilizumab,⁴ theoretically allows the evaluation of bortezomib efficacy by targeting long-lived plasma cells. Follow-up was continued for long enough (13–20 months post-onset) to evaluate the mRS score improvement considering the disease course of anti-NMDAR encephalitis.¹ However, several limitations of this study should be considered when interpreting the results. This was an open-label study conducted using a small number of patients that used only a historical control group. Antibody titers were not tested in other treatment periods, which would have helped to determine the general trend. The study was conducted without completely standardized pretreatment strategies, and there was also some variation in the bortezomib treatment regimen. Long-term outcomes were particularly prone to be confounded by subsequent immunotherapies. Bortezomib-associated adverse events might be underestimated due to the severely impaired consciousness of these patients.

This study re-confirmed the tolerability of bortezomib in patients with anti-NMDAR encephalitis, even after and concurrent with fairly aggressive immunotherapy. However, use of bortezomib did not result in meaningful

clinical improvements compared with a historical control group or in substantial changes in anti-NMDAR antibody titers during follow-up observation periods. Some improvements after bortezomib were not compared to the appropriate control group, and therefore, it is not clear whether bortezomib had any effect or whether the improvements were part of the natural disease course. Although the current results do not support using bortezomib in severe refractory patients, the result may not be generalizable to other conditions, such as the early stage or recurrence. Early administration of bortezomib can target plasma cells before crossing the blood–brain barrier and might reduce the total burden of plasma cells and antibodies in the CNS. Bortezomib is also known to exert synergistic effects with rituximab, a proposed mechanism of which is by impairing proteasome-mediated CD20 degradation.²⁷ Given these theoretical advantages, effects in other autoimmune diseases, and tolerability under the condition of anti-NMDAR encephalitis, further studies are warranted to evaluate whether bortezomib provides benefits in different clinical conditions.

Acknowledgments

None.

Author Contribution

Y.-W.S. contributed to the initial conception and design, collected the data, interpreted the results, wrote the first draft of the manuscript, and revised the manuscript. S.-T.L. contributed to the initial conception and design, collected the data, interpreted the results, revised the manuscript, and supervised all aspects of the study. T.-J.K., J.-S.J., and K.C. contributed to the initial conception and design, interpreted the results and revised the manuscript.

Conflict of Interest

No conflicting relationship exists for any of the authors.

References

1. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol* 2013;12:157–165.
2. Nosadini M, Mohammad SS, Ramanathan S, et al. Immune therapy in autoimmune encephalitis: a systematic review. *Expert Rev Neurother* 2015;15:1391–1419.
3. Lee WJ, Lee ST, Byun JI, et al. Rituximab treatment for autoimmune limbic encephalitis in an institutional cohort. *Neurology* 2016;86:1683–1691.
4. Shin YW, Lee ST, Park KI, et al. Treatment strategies for autoimmune encephalitis. *Ther Adv Neurol Disord* 2018;11:1–19.
5. Lee WJ, Lee ST, Moon J, et al. Tocilizumab in autoimmune encephalitis refractory to rituximab: an Institutional Cohort Study. *Neurotherapeutics* 2016;13:824–832.
6. Lim JA, Lee ST, Moon J, et al. New feasible treatment for refractory autoimmune encephalitis: low-dose interleukin-2. *J Neuroimmunol* 2016;299:107–111.
7. Hiepe F, Dorner T, Hauser AE, et al. Long-lived autoreactive plasma cells drive persistent autoimmune inflammation. *Nat Rev Rheumatol* 2011;7:170–178.
8. Meister S, Schubert U, Neubert K, et al. Extensive immunoglobulin production sensitizes myeloma cells for proteasome inhibition. *Cancer Res* 2007;67:1783–1792.
9. Titulaer MJ, Kayser MS, Dalmau J. Authors' reply. *Lancet Neurol* 2013;12:425–426.
10. Behrendt V, Krogias C, Reinacher-Schick A, et al. Bortezomib treatment for patients with anti-N-methyl-D-aspartate receptor encephalitis. *JAMA Neurol* 2016;73:1251–1253.
11. Scheibe F, Pruss H, Mengel AM, et al. Bortezomib for treatment of therapy-refractory anti-NMDA receptor encephalitis. *Neurology* 2017;88:366–370.
12. Sveinsson O, Granqvist M, Forslin Y, et al. Successful combined targeting of B- and plasma cells in treatment refractory anti-NMDAR encephalitis. *J Neuroimmunol* 2017;312:15–18.
13. Bartolini L, Muscal E. Differences in treatment of anti-NMDA receptor encephalitis: results of a worldwide survey. *J Neurol* 2017;264:647–653.
14. Lee SK, Lee ST. The laboratory diagnosis of autoimmune encephalitis. *J Epilepsy Res* 2016;6:45–50.
15. Sunwoo JS, Chu K, Byun JI, et al. Intrathecal-specific glutamic acid decarboxylase antibodies at low titers in autoimmune neurological disorders. *J Neuroimmunol* 2016;290:15–21.
16. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016;15:391–404.
17. Reeder CB, Reece DE, Kukreti V, et al. Once- versus twice-weekly bortezomib induction therapy with CyBORd in newly diagnosed multiple myeloma. *Blood* 2010;115:3416–3417.
18. Bringhen S, Larocca A, Rossi D, et al. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. *Blood* 2010;116:4745–4753.
19. Guy W. Clinical Global Impression Scale. In: *The ECDEU Assessment Manual for Psychopharmacology-Revised*. Rockville MUDH, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976:218–222. DHEW publication ADM 76-338.

20. Common Terminology Criteria for Adverse Events (CTCAE v4.0). Available: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed 2017, December 20.
21. Gresa-Arribas N, Titulaer MJ, Torrents A, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol* 2014;13:167–177.
22. Alexander T, Sarfert R, Klotsche J, et al. The proteasome inhibitor bortezomib depletes plasma cells and ameliorates clinical manifestations of refractory systemic lupus erythematosus. *Ann Rheum Dis* 2015;74:1474–1478.
23. Jakez-Ocampo J, Atisha-Fregoso Y, Llorente L. Refractory primary Sjogren syndrome successfully treated with bortezomib. *J Clin Rheumatol* 2015;21:31–32.
24. Eskazan AE. Bortezomib therapy in patients with relapsed/refractory acquired thrombotic thrombocytopenic purpura. *Ann Hematol* 2016;95:1751–1756.
25. Zhang C, Tian DC, Yang CS, et al. Safety and efficacy of bortezomib in patients with highly relapsing neuromyelitis optica spectrum disorder. *JAMA Neurol* 2017;74:1010–1012.
26. Schneider-Gold C, Reinacher-Schick A, Ellrichmann G, Gold R. Bortezomib in severe MuSK-antibody positive myasthenia gravis: first clinical experience. *Ther Adv Neurol Disord* 2017;10:339–341.
27. Verbrugge SE, Scheper RJ, Lems WF, et al. Proteasome inhibitors as experimental therapeutics of autoimmune diseases. *Arthritis Res Ther* 2015;17:17.
28. Martinez-Hernandez E, Horvath J, Shiloh-Malawsky Y, et al. Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis. *Neurology* 2011;77:589–593.
29. Foran E, Kwon DY, Nofziger JH, et al. CNS uptake of bortezomib is enhanced by P-glycoprotein inhibition: implications for spinal muscular atrophy. *Neurobiol Dis* 2016;88:118–124.
30. Ruegg S, Irani SR. The trouble with plasma cells: getting to the root cause. *Neurology* 2017;88:340–341.
31. Planaguma J, Haselmann H, Mannara F, et al. Ephrin-B2 prevents N-methyl-D-aspartate receptor antibody effects on memory and neuroplasticity. *Ann Neurol* 2016;80:388–400.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Clinical responses after bortezomib treatment.

Table S2. Clinical characteristics and outcome of the control population.