Bortezomib for treatment of therapy-refractory anti-NMDA receptor encephalitis

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ABSTRACT

Objective: We assessed the therapeutic potential of the plasma-cell-depleting proteasome inhibitor bortezomib in severe and therapy-refractory cases of anti–NMDA receptor (anti-NMDAR) encephalitis.

Methods: Five severely affected patients with anti-NMDAR encephalitis with delayed treatment response or resistance to standard immunosuppressive and B-cell-depleting drugs (corticosteroids, IV immunoglobulins, plasma exchange, immunoadsorption, rituximab, cyclophosphamide) who required medical treatment and artificial ventilation on intensive care units were treated with 1–6 cycles of 1.3 mg/m^2 bortezomib. Occurrence of adverse events was closely monitored.

Results: Bortezomib treatment showed clinical improvement or disease remission, which was accompanied by a partial NMDAR antibody titer decline in 4 of 5 patients. With respect to disease severity, addition of bortezomib to the multimodal immunosuppressive treatment regimen was associated with an acceptable safety profile.

Conclusions: Our study identifies bortezomib as a promising escalation therapy for severe and therapy-refractory anti-NMDAR encephalitis.

Classification of evidence: This retrospective case series provides Class IV evidence that bortezomib reduces antibody titers and improves the clinical course of patients with severe anti-NMDAR encephalitis. *Neurology*® 2017;88:366–370

GLOSSARY

ICU = intensive care unit; **IgG** = immunoglobulin G; **IVIg** = IV immunoglobulins; **NMDAR** = NMDA receptor; **SLE** = systemic lupus erythematosus.

Severe courses of anti–NMDA receptor (anti-NMDAR) encephalitis are complicated by persisting status epilepticus or life-threatening autonomic dysfunction requiring intensive care unit (ICU) support with mechanical ventilation and long-term sedation.[1] These malignant courses remain refractory to standard immunosuppressive and B-cell-depleting treatments like corticosteroids, IV immunoglobulins (IVIg), cyclophosphamide, rituximab, plasma exchange, or immunoadsorption. Therapy resistance is associated with insufficient anti-NMDAR antibody titer reduction,[2] hence the pathobiology behind this phenomenon remains elusive. As known from other autoimmune diseases like systemic lupus erythematosus (SLE), especially long-lived plasma cells contribute to therapy resistance by secretion of autoreactive antibodies.[3] The proteasome inhibitor bortezomib depletes plasma cells, has been approved for treatment of multiple myeloma, and had promising results with off-label application in in SLE[4] or Sjögren syndrome.[5] Despite the risks of polyneuropathy, cytopenia, and infections, we investigated the therapeutic potential of bortezomib in 5 patients with severe anti-NMDAR encephalitis and observed improved disease control associated with swift NMDAR antibody titer decline associated with an acceptable safety profile.

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METHODS **Patients.** This retrospective case series of 5 patients examined the therapeutic potential of bortezomib in therapy-refractory anti-NMDAR encephalitis. Patients 1 and 2 were young women without known neoplasms, patients 3 and 4 with

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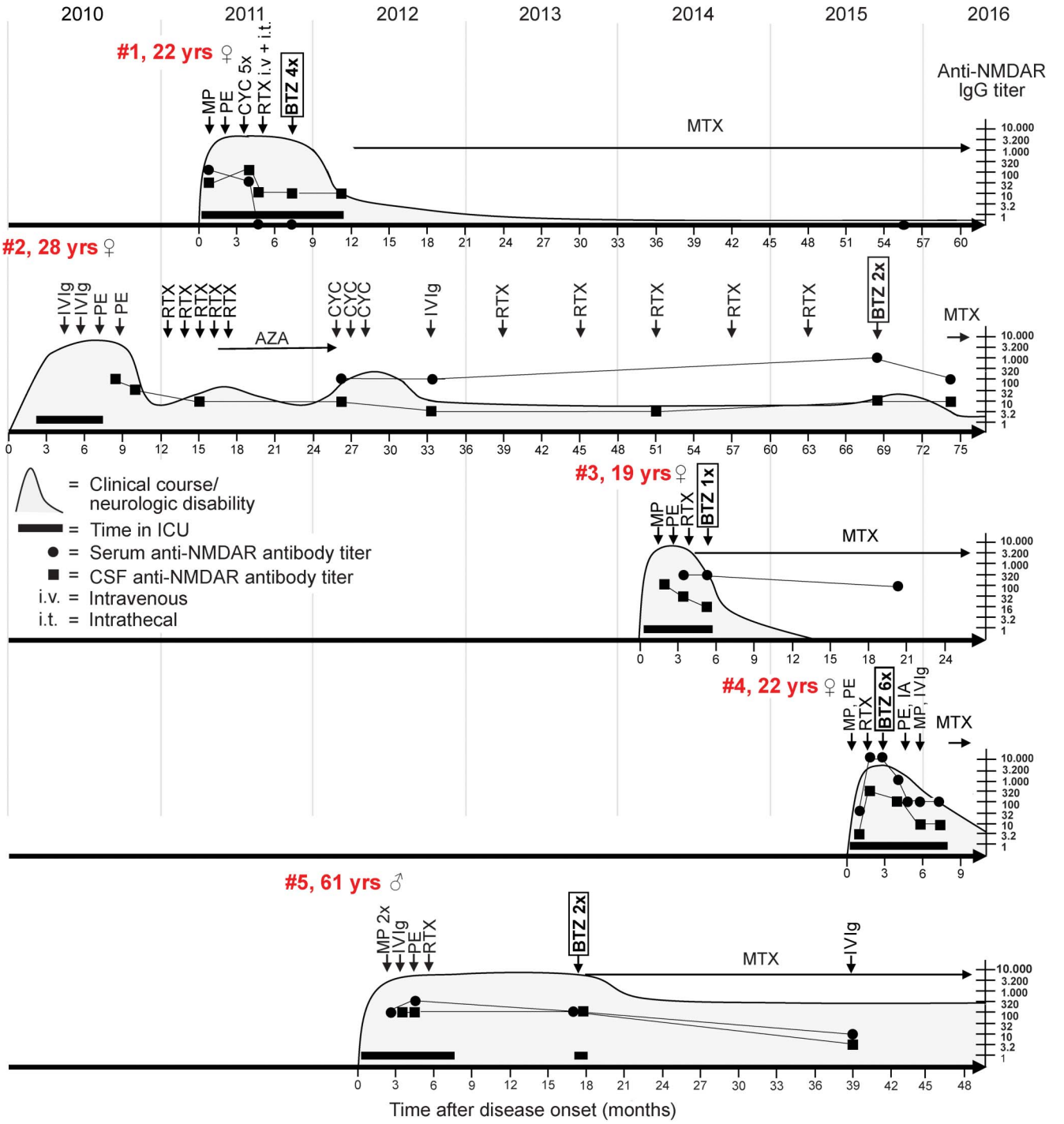
ovarian teratoma–associated disease variants. Patient 5 had acute necrotizing encephalitis with profound defects in MRI. Extensive diagnostic workup could not clarify whether this primary encephalitis presented as acute hemorrhagic leukoencephalitis (Hurst disease) or herpes encephalitis (for details, see table e-1 at Neurology.org). After ICU treatment for several months, the patient persisted in a vegetative state and developed orofacial dyskinesias with therapy-refractory epilepsy. Evidence of NMDAR antibodies in serum and CSF led to diagnosis of secondary anti-NMDAR encephalitis.

The figure and table e-1 summarize detailed patient histories with clinical course, diagnostic workup, treatment regimens, and

Figure **Clinical course with relapses, applied immunotherapy, and NMDA receptor (NMDAR) antibody titers of 5 patients with severe anti-NMDAR encephalitis treated with bortezomib**



Clinical course is shown by an arbitrary scale considering several measures of disease severity, such as ventilator dependency, status epilepticus/frequency of seizures, autonomous dysregulation, severity of psychosis, severity of movement disorder, and requirement for treatment on intensive care unit (ICU), intermediate care unit, or regular ward. NMDAR antibody titers measured by an indirect immunofluorescence assay were shown using a nonmetric scaling. AZA = azathioprine; BTZ = bortezomib; CYC = cyclophosphamide; IA = immunoadsorption; IgG = immunoglobulin G; IVIg = IV immunoglobulins; MP = methylprednisolone; MTX = methotrexate; PE = plasma exchange; RTX = rituximab.

clinical outcomes. Tables e-2–e-5 present antiepileptic drug therapy, NMDAR antibody titers before and after rituximab and bortezomib therapy, serum immunoglobulin G (IgG), CSF IgG index, and CSF oligoclonal bands before and after bortezomib therapy, as well as time intervals between immunotherapies. All patients had very severe anti-NMDAR encephalitis that required artificial ventilation and long-term ICU stays. The study provides Class IV evidence for bortezomib effectiveness.

NMDAR antibody testing. NMDAR antibody testing was performed by indirect immunofluorescence assay or by BIOCHIP mosaic technology (Euroimmun, Lübeck, Germany; or Labor Berlin, Germany). Titers of at least 1:1 in CSF and higher than 1:10 in serum together with the compatible clinical phenotype were regarded as pathologic.

Bortezomib treatment regimen. From November 2011 to February 2016, 5 patients with anti-NMDAR encephalitis refractory to standard immunosuppressive treatment approaches (methylprednisolone, plasma exchange, immunoadsorption, IVIg, rituximab, cyclophosphamide) were treated with 1–6 cycles of bortezomib (Velcade; Janssen-Cilag, Neuss, Germany), each lasting 21 days. A total of 1.3 mg/m^2 bortezomib were administered on days 1, 4, 8, and 11 combined with 20 mg IV dexamethasone each. On the injection-free days, patients received 10 mg oral prednisolone. Bortezomib was administered IV to patient 1, but because of improved tolerability, all other patients received subcutaneous injections.[6] Concomitant infection prophylaxis consisted of 200 mg acyclovir daily and 960 mg cotrimoxazole three times weekly. Drug safety was evaluated by monitoring adverse events.

Standard protocol approvals, registrations, and patient consents. Written informed consent for bortezomib treatment was given by patients' next of kin. Patients or next of kin gave their written consent to publication.

RESULTS Patient 1 exhibited anti-NMDAR encephalitis with a marked sympathetic hyperactivity syndrome and high seizure frequency requiring long-term sedation for 10 months. Over 8 months, the patient remained unresponsive to methylprednisolone, IVIg, plasma exchange, rituximab, and cyclophosphamide, but showed remarkable clinical improvement with sedation withdrawal and respirator weaning after 4 cycles of bortezomib. Patient 2 had persisting status epilepticus that required mechanical ventilation and intensive care treatment for 5 months. After immunotherapy with IVIg and plasma exchange, the patient improved, but frequent relapses required cyclophosphamide, rituximab, and IVIg therapy. A neurocognitive defect syndrome persisted over several years but showed mild improvement after therapy escalation with 2 cycles of bortezomib. Patient 3 improved after teratomectomy and immunosuppressive therapy with methylprednisolone, plasma exchange, and rituximab. She accomplished respirator weaning and physical rehabilitation within 3 months, but recovery was hampered by severe neuropsychiatric symptoms. Application of one cycle of bortezomib enabled swift control of neuropsychiatric outbursts, and neurocognitive deficits improved, subsequently leading to complete clinical remission. Patient 4 presented with extremely high NMDAR antibody titers and teratomectomy, methylprednisolone, plasma exchange, immunoadsorption, IVIg, and rituximab treatment showed no effect on persisting status epilepticus and severe movement disorder. Escalation of standard therapy with 6 cycles of bortezomib induced marked NMDAR antibody titer reduction followed by delayed clinical improvement, allowing respirator weaning, sedation withdrawal, and referral to rehabilitation after 7 months. Patient 5 had secondary anti-NMDAR encephalitis triggered by severe acute necrotizing encephalitis. The patient remained therapy-refractory to high-dose methylprednisolone, IVIg, plasma exchange, and rituximab and persisted in a vegetative state for 1 year. After treatment with 2 cycles of bortezomib, NMDAR antibody levels markedly decreased, the patient improved to minimally conscious state, orofacial dyskinesias remitted, and a much-reduced seizure frequency allowed distinct antiepileptic drug withdrawal.

With respect to disease severity, bortezomib had an acceptable safety profile. Patients 3 and 5 exhibited no side effects. Patient 2 did not receive the last bortezomib dose of both cycles due to infection, fever, and thrombocytopenia. Drug polypharmacy in combination with bortezomib-associated liver enzyme increase required bortezomib dose reduction from 1.3 to 1.0 mg/m^2 for some cycles in patients 1 and 4. Patient 1 developed a bortezomib-associated neuropathy, which fully resolved over time. Patient 4 already presented with critical illness neuropathy before bortezomib treatment without evidence of deterioration after 6 cycles of bortezomib. Following multimodal immunotherapy, microbiological routine testing identified in patient 4 an asymptomatic, atypical blood mycobacteriosis, which fully resolved after antibiotic therapy.

DISCUSSION To improve treatment concepts of anti-NMDAR encephalitis, we complemented standard first-line and second-line therapies with the proteasome inhibitor bortezomib and found partial NMDAR antibody titer decline and subsequent clinical improvement accompanied by an acceptable risk profile.

As bortezomib inhibits NF-κB activation and the ubiquitin-proteasome system, it affects differentiation, survival, and function of several immune cells, but the high rate of antibody synthesis predisposes especially plasma cells to apoptotic cell death.[7] Plasma cell–mediated and antibody-mediated mechanisms are considered for anti-NMDAR encephalitis where NMDAR antibodies trigger disease by internalization

of NMDAR into neurons. However, autopsy studies suggested that NMDAR antibodies are not only produced in the periphery, but also in the brain by resident plasma cells in perivascular, interstitial, and Virchow-Robin spaces.[8] Although bortezomib might only barely cross the blood–brain barrier[9,10] and its intrathecal application is lethal,[11] it remains open whether bortezomib might tackle plasma cells producing NMDAR antibodies in the periphery as well as in the CNS.

However, knowledge from other autoimmune diseases contributes to an understanding of bortezomib effectiveness in anti-NMDAR encephalitis: short-lived and long-lived plasma cells maintain humoral autoimmunity through secretion of autoreactive antibodies.[3] While short-lived plasma cells originate from activated B cells, they can be indirectly targeted by B-cell depletion with rituximab. In contrast, long-lived plasma cells are usually resistant to conventional immunosuppressive and B-cell-depleting therapies.[12] Thus, persisting autoreactive antibodies after rituximab might be attributed to long-lived plasma cells. As shown in patients with SLE, bortezomib targets both plasma cell compartments and depletes ~30% of plasma cells within the bone marrow, leading to clinical improvement after 1 to 2 treatment cycles.[4] Hence, the combinational approach of bortezomib and rituximab not only depletes short-lived and long-lived plasma cells, it also attacks plasmablast precursors that might prevent generation[3] and immigration of novel autoreactive B cells and plasma cells into the brain.

Although patients with anti-NMDAR encephalitis present a higher disease severity and require other immunotherapy regimens than patients with multiple myeloma, concerns regarding bortezomib side effects like polyneuropathy should not restrict its application in therapy-refractory anti-NMDAR encephalitis, especially since standard therapy with cyclophosphamide is also accompanied by a high risk of infections/sepsis, infertility, and development of secondary tumors.

Our study has several limitations: it is an uncontrolled retrospective study with a small sample size and heterogeneous pretreatment and courses of disease. Moreover, cycle numbers of bortezomib administration differed in our patients, mainly attributed to a diverging disease severity with differences in the individual plasma cell autoimmunity (e.g., plasma cell subpopulations, levels, and locations) that resulted in a different speed of therapy response. The other applied immunotherapies are confounders when attributing bortezomib treatment for clinical improvement and NMDAR antibody titer decrease. Therefore, neither a natural remission nor a delayed treatment response following standard immunotherapies could be excluded. However, clinical improvements were only observed in all patients after application of at least 1 or 2 bortezomib cycles, which was most remarkable in patients 2 and 5 considering the time window between applied treatments. Thus, our data suggest that severe courses of anti-NMDAR encephalitis benefit from timely therapy escalation with bortezomib, coupled with a favorable safety profile.

Although even standard treatment approaches such as cyclophosphamide or rituximab have not been tested in clinical trials of autoimmune encephalitis, our findings warrant clinical studies of bortezomib in the management of autoimmune encephalitis.

AUTHOR CONTRIBUTIONS

F.S. and A.M. developed the study concept and wrote the article. F.S., H.P., A.M., S.K., A.N., M.K., K.R., T.A., F.H., and A.M. contributed to patient clinical care and data collection and analysis.

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DISCLOSURE

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