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Review Article

Neurocritical care for Anti-NMDA receptor encephalitis

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ABSTRACT

In this review, we summarize the clinical presentations of the acute stage of anti-N-methyl-D-aspartate (NMDA) receptor encephalitis and the neurocritical care strategy in intensive care units. Anti-NMDA receptor encephalitis has characteristic clinical features and is predominantly seen in young adults and children. Most patients have five stages of clinical presentation, including a prodromal phase, psychotic and/or seizure phase, unresponsive and/or catatonic phase, hyperkinetic phase, and gradual recovery phase. The clinical course usually begins with viral infection-like symptoms that last for up to 2 weeks (prodromal phase), followed by the rapid development of schizophrenia-like psychiatric symptoms and seizures (psychotic and seizure phase). Patients may have a decreased level of consciousness with central hypoventilation, frequently requiring mechanical ventilation. In the subsequent hyperkinetic phase, patients present with orofacial-limb dyskinesia and autonomic instability. Children with significant neurological symptoms of anti-NMDA receptor encephalitis should initially be managed in a pediatric intensive care unit. The acute critical presentations are, refractory seizures, autonomic dysfunction, hypoventilation, cardiac arrhythmia, and hyperkinetic crisis. Symptom-guided therapies and critical care are necessary in the acute stage to improve the prognosis.

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Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a disorder with characteristic clinical features that is predominantly seen in young adults and children with or without teratomas [1,2]. Most patients have five stages of clinical presentation: a prodromal phase, psychotic and/or seizure phase, unresponsive and/or catatonic phase, hyperkinetic phase, and gradual recovery phase [3,4]. Some of the symptoms may not appear in sequence as with a typical course. Furthermore, they may appear together making the treatment more complicated. The clinical course usually begins with viral infection-like symptoms that last for up to 2 weeks (prodromal phase), followed by the rapid development of schizophrenia-like psychiatric symptoms and seizures (psychotic and seizure phase). Subsequently, in the unresponsive and/or catatonic phase, the patients become mute and unresponsive but awake in an akinetic state. They may also have a decreased level of consciousness with central hypoventilation, frequently requiring mechanical ventilation. In the following hyperkinetic phase, they present with orofacial-limb dyskinesia and autonomic instability. Finally, the patients enter into a gradual recovery phase, but in some there is a possibility of relapse [1–6].

Anti-NMDA receptor encephalitis is mainly mediated by autoantibodies against the GluN1 subunit of the receptor. In the acute phase, the pathologies of brain have shown infiltrates of B cells, plasma cells, CD4 T cells and less frequently CD8 T cells. There are also microglial activation, deposits of immunoglobulin G, and little or no neuronal loss [7–9]. The antibodies synthesized systemically can crosslink the NMDA receptors by crossing the blood-brain barrier [10–13]. They alter the surface dynamics and interaction with other synaptic proteins, and causing their internalization along with severe impairment of synaptic plasticity and NMDA receptor network function [14–17].

Children with significant neurological symptoms of anti-NMDA receptor encephalitis should be initially managed in a pediatric intensive care unit as status epilepticus, refractory seizures, autonomic dysfunction, hypoventilation, cardiac arrhythmia, and hyperkinetic crisis may occur. Neurocritical care for children with anti-NMDA receptor encephalitis requires early intervention by an interdisciplinary team including intensivists, neurologists, psychiatrists, cardiologists, nutritionists, physical therapists, social workers, physiatrists, pastoral care, and child life experts. Early diagnosis, symptom-guided therapies and critical care are necessary in the acute stage to improve the prognosis (Fig. 1) [18–20].

Clinical manifestations and neurocritical care in the acute stage

The discovery of anti-NMDA receptor encephalitis made it possible to recognize that some patients with rapidly progressive psychiatric symptoms or cognitive impairment, seizures, abnormal movements, or coma of unknown cause have an autoimmune disease. In this disease, autoantibodies serve as a diagnostic marker and alter NMDA receptor-related synaptic transmission. At symptom onset, distinguishing the disease from a primary psychiatric disorder, movement disorder, or viral encephalitis-related status epilepticus is challenging. The severity of symptoms often requires intensive care [21].

The major clinical intensive care unit problems include disturbance of consciousness, autonomic dysfunction, seizures/status epilepticus, movement disorder/hyperkinetic status, and other complications such as septic shock, organ failure, increase in intracranial pressure, resuscitation, surgical complications, psychiatric complications, and ethical conflicts [22].

When there is high clinical suspicion of the disease, rapid stage-based treatment should be initiated as early as possible since confirmatory testing is not performed at some centers and may take days to weeks [23,24]. The known pathophysiology and current evidence suggests that starting therapy as soon as possible may lead to better outcomes. With appropriate treatment, substantial improvements or complete recovery have been reported in up to 75% of patients [1,25]. At 24 months' follow-up of the cohort study by Titulaer et al., 203 (81%) patients had good outcome. Outcomes continued to improve for up to 18 months after symptom onset. Predictors of good outcome were early treatment and no admission to an intensive care unit [25]. However, approximately 12–25% of children will have a relapse even after resolution [25,26].

Detection of the underlying etiology and infectious pathogens

Since the initial presentations of anti-NMDA receptor encephalitis mimic those of viral encephalitis and other autoimmune encephalitis, a differential diagnosis should be made as soon as possible. An increasing number of studies have identified associations between antineuronal antibodies to ion channels, receptors, other synaptic proteins and central nervous system disorders, and especially their role in pediatric encephalitis [27]. They are classified according to the location of their respective antigens as (1) intracellular antigens, and (2) cell membrane ion channels or surface antigens [28]. On the other hand, many studies have reported that infectious pathogens can co-exist with antineuronal antibodies in patients with autoimmune encephalitis [29], of which herpes simplex virus has been reported to be associated with anti-NMDA receptor encephalitis [30]. Therefore, detecting antineuronal antibodies and possible infectious pathogens is important in the acute stage. Dalmau et al. reported the first 100 patients with anti-NMDA receptor encephalitis (91 female patients), and they mainly had psychiatric presentations. Of the 98 patients who underwent screening, 59% had tumors, most of which were ovarian teratomas [1]. Therefore, screening for ovary tumors should be performed in all female patients with anti-NMDA receptor encephalitis, including children and adults. Removing the tumor is the best therapy for anti-NMDA receptor encephalitis.

The outcome of autoimmune encephalitis generally depends on the underlying causes. Identifying the possible infectious pathogens and clarifying the underlying immunological pathogenic entity (such as a removable tumor, a treatable viral infection, antineuronal antibodies, or a combination of a virus infection and immune-mediated process) is

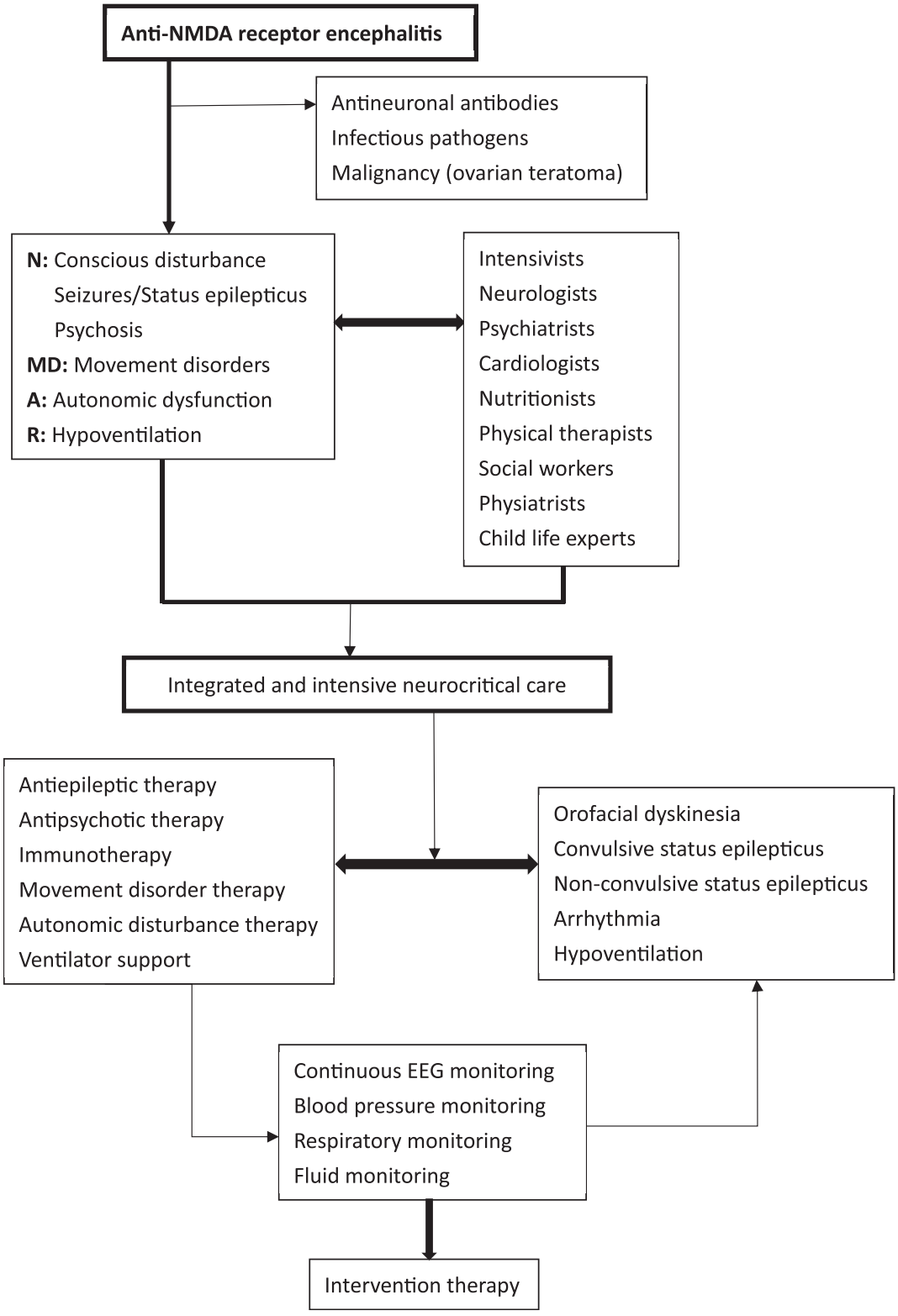

Fig. 1 Children with anti-NMDA receptor encephalitis require early interventions and neurocritical care by an interdisciplinary team. Members of the medical team should include intensivists, neurologists, psychiatrists, cardiologists, nutritionists, physical therapists, social workers, physiatrists, pastoral care, and child life experts. A multimodal approach with intensive care facilities, symptom-guided therapies and critical care are necessary in the acute stage to improve the prognosis.

very important in the management of anti-NMDA receptor encephalitis [27].

Neuroimaging findings

The frequency of abnormal findings on magnetic resonance imaging (MRI) in anti-NMDA receptor encephalitis have been reported with a wide range of 11%–83% [7,31,32]. The typical features of abnormalities may include T2/fluid attenuation inversion recovery hyperintensity of the medial temporal lobe, frontal lobe subcortical white matter and periventricular region as well as leptomeningeal and cortical contrast enhancement [31]. Progressive cerebellar atrophy on MRI is a poor prognostic marker [33]. However, a negative MRI should not be a reason to discount a possible diagnosis of anti-NMDA receptor encephalitis. The studies assessing fludeoxyglucose-positron emission tomography (FDG-PET) in anti-NMDA receptor encephalitis indicate that this technique may be able to detect abnormalities in cases with normal brain MRI studies [31]. Typical findings on FDG-PET in the acute phase of the illness may include fronto-temporal hypermetabolism and occipito-parietal hypometabolism [31,34].

Seizures, electroencephalogram and intensive monitoring

Seizures are a common presentation of anti-NMDA receptor encephalitis in children and young men [21,25,35,36]. Approximately 70% of patients develop seizures, with reported frequencies of 57–82% [1,25,36–38]. Seizures as the sole manifestation occurs in only 23% of children, in contrast to adults in whom seizures are the main presenting symptom in anti-NMDA receptor encephalitis [37]. Therefore, pediatricians should be aware of the possibility of anti-NMDA receptor encephalitis when treating a child presenting with seizures and encephalopathy. In the acute stage, Liu et al. reported the following types and frequency of seizures: single seizure (17/88, 19.3%), repetitive seizures (27/88, 30.7%), non-refractory status epilepticus (22/88, 25%), refractory status epilepticus (13/88, 14.8%), and super refractory status epilepticus (9/88, 10.2%). In addition, they reported that seizures were more likely to recur in patients with a tumor, development of status epilepticus, coma, or intensive care unit admission in the acute stage ($p < 0.05$). More than 80% of their patients with anti-NMDA receptor encephalitis and acute seizures had their last seizure within 6 months of disease onset. Moreover, seizure freedom was observed within 2 years in all patients [36]. Because the seizures are provoked by a specific and treatable autoimmune mechanism, there is a debate over the term "autoimmune epilepsy" during the disease [39]. Although seizures in anti-NMDA receptor encephalitis have a favorable outcome, a progressive frequency of seizures in the acute stage requires escalation of antiepileptic drugs, immunotherapy and intensive care monitoring.

There are three characteristic electroencephalogram patterns in anti-NMDA receptor encephalitis: excessive beta activity range 14–20 Hertz, extreme delta brush, and generalized rhythmic delta activity [34]. Although not specific, these patterns are suggestive, and their recognition can help to make an earlier diagnosis of the disorder. Extreme delta brush occurs in up to 30% of patients with anti-NMDA receptor encephalitis [19,40], however the clinical significance of extreme delta brush should be interpreted with caution. For clinical management, movement disorders and authentic seizures should be considered and identified in this stage and treated with different strategies. A differential diagnosis is sometimes very difficult, particularly in comatose patients. Almost all kinds of dyskinesia have been observed, including mastication, grimacing, ballistic or dystonic movements, stiffness and myoclonus [4,41]. Generalized rhythmic delta activity has been reported to be significantly associated with abnormal movements and to differ from epileptic activity [42]. Video-electroencephalogram is highly recommended in difficult cases. If there is doubt over the diagnosis, invasive techniques should be considered in these complex situations, such as intracranial pressure monitoring and intracerebral electroencephalography [43].

Frequent electroencephalogram monitoring from the onset of disease is a key step to detect these patterns and electrographic seizures. Moreover, generalized rhythmic delta activity must not be misinterpreted as seizures, status epilepticus or non-convulsive status epilepticus, as this would lead to an increase in the administration of antiepileptic drugs and so worsen awareness [40].

Antiepileptic therapy

In the study of de Bruijn et al., 40 of 42 patients with anti-NMDA receptor encephalitis were treated with levetiracetam (n = 28), valproic acid (n = 24), or carbamazepine (n = 10). These antiepileptic drugs were combined in 17 patients. The majority (93%) of the patients were treated with a combination of antiepileptic drugs and immunotherapy [38]. In the study by Haberlandt et al., 88% of the patients received antiepileptic drugs, of whom 20% were given monotherapy and 80% received up to eight antiepileptic drugs in various combinations [44]. Comparing the patients who were treated with antiepileptic drugs to those who were treated with immunotherapy, those who received immunotherapy were more likely to achieve seizure freedom [38].

Other than traditional antiepileptic drugs, Santoro et al. reported that ketamine is a useful adjunct treatment for super-refractory status epilepticus in patients with anti-NMDA receptor encephalitis [45]. They suggested that a ketamine treatment protocol of administering a loading dose followed by maintenance infusion (0.05 mg/kg/min infusion) could result in clinical and/or electrographic seizure cessation in less than 48 h. Moreover, epilepsy outcomes were favorable from a seizure freedom standpoint, and earlier treatment was associated with better epilepsy outcomes [45].

Pillai et al. did not observe drug-resistant epilepsy in a cohort study of patients with anti-NMDA receptor encephalitis. Status epilepticus, focal seizures and epileptiform discharges during acute encephalitis episodes have been identified as risk factors for pharmacoresistant epilepsy [44,46].

Antipsychotic therapy

Catatonia, a neuropsychiatric syndrome involving a combination of mental, motor, speech, vegetative, and behavioral signs,

has been increasingly reported to be a part of the clinical presentation of anti-NMDA receptor encephalitis [47,48]. The most common presenting signs are immobility (motor inhibition), staring, mutism, posturing, withdrawal, and rigidity [47]. Antipsychotics, such as haloperidol, must be used with caution because of the possibility of exacerbating movement disorders in patients in the later stages of the disease with catatonia [2,4,49]. A test dose of lorazepam (1 mg–2 mg) can be used to confirm the diagnosis of catatonia [50]. Benzodiazepines or rarely electroconvulsive therapy have been reported to be effective treatments for catatonia [2,51–53].

Few studies have focused on the treatment of psychiatric symptoms such as mood lability, aggression, impulsivity, and hallucinations [49]. Typical and atypical antipsychotics have been used with limited success for aggression and hallucinations. In extreme cases of agitation, phenobarbital and fentanyl have been used to induce a medical coma. Chapman et al. reported improvements in sleep-cycle regulation with clonidine, trazodone, and benzodiazepines. For mood dysregulation, valproic acid, gabapentin and lithium have shown only a minor effect [54–57]. In addition, Florance et al. reported that a 6-year-old boy with hyperactivity and impulsivity was responsive to psychostimulants [2]. Clonidine, trazodone and benzodiazepines are used to target sleep cycle dysregulation, and phenobarbital, trihexyphenidyl and opioids are used for extreme agitation [51,52,58–61]. Methotrimeprazine or dexmedetomidine infusion may be beneficial for both intubated and non-intubated patients with refractory agitation [18].

Autonomic dysfunction and hypoventilation

It is difficult to manage autonomic and hemodynamic instability in patients with anti-NMDA receptor encephalitis. Arrhythmia is a frequent presentation, and resting tachycardia has also been widely reported in pediatric patients. However, it is challenging to manage severe bradycardia and asystole events which may be exacerbated by vagal stimulation. The use of a foley catheter, bowel regimens to prevent constipation, and careful suctioning of the endotracheal tube are essential to minimize parasympathetic stimulation. In addition, continuous electroencephalogram monitoring has been used to prevent seizures from inducing bradycardia [1,2,18,62–65]. Glycopyrrolate or theophylline may be considered to prevent severe bradycardia [66]. If severe bradycardia is frequent and unresponsive to medical therapies, an implantable pacemaker may be considered [67]. In patients with new onset bradycardia, brain imaging can be used to rule out hydrocephalus [4]. It is especially important to remember that this is part of the condition, which will improve as definitive treatment takes effect [68].

Autonomic dysfunction also manifests as impaired temperature or blood pressure regulation. While patients are being maintained on immunosuppressant therapies, infectious etiologies for hypothermia/hyperthermia must be considered. Movement disorders are often exacerbated during a febrile state, and therefore aggressive temperature control should be implemented with antipyretics, environmental cooling, and cooling blankets as indicated [18]. On the other hand, the use of antimicrobial agents should be avoided unless a source of sepsis is identified; and specific physiological parameters should be treated if they are persistent or cause significant compromise [68].

Hypoventilation in intensive care unit patients with anti-NMDA receptor encephalitis may make it difficult to wean from mechanical ventilation, because delirium, agitation, and movement disorders may require heavy sedation. Placement of tracheostomy and gastrostomy tubes in the third week after the diagnosis may improve patient safety and allow for less sedation and earlier rehabilitation [18]. In addition, the occurrence of hypersalivation has also been reported [20,69]. Clinicians should therefore pay particular attention to managing tracheostomy complications due to salivary contamination of tracheostomy wounds [20].

Immunotherapy

Anti-NMDA receptor encephalitis can be reversed and treated with an early diagnosis and appropriate therapy. The most well-known treatment for this autoimmune disorder is immunomodulation [25,70]. First-line immunotherapy includes intravenous high-dose steroids (methylprednisolone), intravenous immunoglobulin, and/or plasmapheresis. Removing the tumor is indicated in some cases. New regimens or second-line immunotherapy for those who do not respond well to the first-line treatment includes targeted B-cell therapy with rituximab and cyclophosphamide (an alkylating agent which directly inhibits T cell and B cell proliferation) [6,25,70].

Nevertheless, malignant courses remain refractory to standard immunosuppressive and B-cell-depleting treatments. Therapy resistance has been associated with an insufficient reduction in anti-NMDA receptor antibody titer [71]. Scheibe et al. investigated the therapeutic potential of bortezomib in five patients with severe anti-NMDA receptor encephalitis in a retrospective case series, and observed improved disease control associated with a swift decline in NMDA receptor antibody titer. Moreover, the safety profile was acceptable, and the study provided Class IV evidence that bortezomib can reduce antibody titers and improve the clinical course of patients with severe anti-NMDA receptor encephalitis [72].

While short-lived plasma cells originate from activated B cells, they can be indirectly targeted by B-cell depletion with rituximab [68]. In contrast, long-lived plasma cells are usually resistant to conventional immunosuppressive and B-cell-depleting therapies such as rituximab [73]. Bortezomib targets both plasma cell compartments and has been reported to deplete 30% of plasma cells within the bone marrow, leading to clinical improvements after 1 to 2 treatment cycles [74]. Hence, a combination of bortezomib and rituximab not only depletes short-lived and long-lived plasma cells, it also attacks plasmablast precursors which may then prevent the generation and immigration of novel autoreactive B cells and plasma cells into the brain [72,75].

Prediction score

Balu et al. developed the NEOS (anti-NMDA Receptor Encephalitis One-Year Functional Status) score to predict the 1-year outcome of the disease. Five features have been found to be independent predictors of poor functional status 1 year

after symptom onset: (1) need for intensive care unit admission, (2) lack of treatment within 4 weeks of symptom onset, (3) lack of clinical improvement within 4 weeks of starting treatment, (4) abnormal brain magnetic resonance imaging, and (5) elevated white blood cell count in cerebrospinal fluid (>20 cells/μL) [76]. The NEOS score can help to estimate the clinical course following the diagnosis, and may aid in identifying patients who could benefit from novel therapies.

YKL-40 (chitinase 3-like 1 or HCgp39) is a secreted glycoprotein belonging to the glycosyl hydrolase 18 family, responding to acute and chronic inflammation of central nervous system. Cerebrospinal fluid levels of YKL-40 in patients with anti-NMDA receptor encephalitis were increased and correlated with clinical modified Rankin Scale [12]. Leypoldt et al. also reported that 70% of patients with early-stage anti-NMDA receptor encephalitis had an increased concentration of cerebrospinal fluid C-X-C motif chemokine 13 (CXCL13) that correlated with intrathecal NMDA receptor antibody synthesis. In addition, prolonged or secondary elevation of CXCL13 was associated with a limited response to treatment and relapses. Therefore, YKL-40 and CXCL13 may be useful biomarkers of treatment response and outcome in anti-NMDA receptor encephalitis [11,12].

Summary

Anti-NMDA receptor encephalitis is a relatively recently identified condition, however it is quite common and has a wide variety of clinical presentations and responses to treatment. Early recognition and a multidisciplinary approach may provide earlier access to first- and second-line therapies. An integrated and intensive care group is necessary for the management of this challenging disease. Future studies are needed to examine the efficacy of current therapeutic strategies on long-term outcomes.

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Conflicts of interest

The author declares no conflict of interests.

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