Ovarian Teratoma-Associated Anti-N-Methyl-D-Aspartate Receptor Encephalitis: Pathogenesis, Diagnosis, Treatment, and Research Advances Postprint

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Date: 2023-07-25T00:00:00+00:00

Abstract

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune encephalitis and a rare complication of ovarian teratoma, with surgical tumor resection combined with immunotherapy as the main treatment modality; however, the pathogenesis of ovarian teratoma-associated anti-NMDAR encephalitis remains unclear, patients present with diverse clinical manifestations predominantly featuring neurological symptoms, and the condition is prone to misdiagnosis and missed diagnosis, requiring collaborative diagnosis and treatment by gynecologists and neurologists. This article reviews the structure and function of NMDAR, summarizes previous research findings on ovarian teratoma-associated anti-NMDAR encephalitis, outlines research progress on its pathogenesis, early diagnosis, differential diagnosis, treatment, prognosis, and recurrence, and provides theoretical basis and insights for better diagnosis and treatment of ovarian teratoma-associated anti-NMDAR encephalitis.

Full Text

Advances in Pathogenesis, Diagnosis and Treatment of Ovarian Teratoma-Associated Anti-N-Methyl-D-Aspartate Receptor Encephalitis

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Abstract

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune encephalitis that represents a rare complication of ovarian teratoma. The primary treatment is surgical resection of the tumor combined with immunotherapy; however, the pathogenesis of ovarian teratoma-associated anti-NMDAR encephalitis remains unclear. Moreover, patients present with diverse clinical manifestations, predominantly neurological symptoms, which are prone to misdiagnosis and missed diagnosis, requiring collaborative diagnosis and treatment by gynecologists and neurologists. This article reviews the structure and function of NMDAR, summarizes previous research findings on ovarian teratoma-associated anti-NMDAR encephalitis, and outlines research progress in its pathogenesis, early diagnosis, differential diagnosis, treatment, prognosis, and recurrence, aiming to provide a theoretical basis and insights for improved diagnosis and treatment of this condition.

Key words: Anti-N-methyl-D-aspartate receptor encephalitis; Teratoma; Anti-NMDAR antibody encephalitis; Pathogenesis

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Anti-NMDAR encephalitis, first identified as a paraneoplastic limbic encephalitis associated with NMDAR antibodies, is the most common type of paraneoplastic neurological syndrome caused by ovarian teratoma (OT), with an incidence of 5-8 per 100,000. Dalmau et al. [1] first isolated anti-NMDAR antibodies from the serum and cerebrospinal fluid of patients with OT presenting neuropsychiatric symptoms in 2007. Cohort studies have shown that among 577 patients with anti-NMDAR encephalitis, 38% had associated tumors, of which 94% were OT, 2% were extragonadal teratomas, and 4% were other tumors [2].

OT-associated anti-NMDAR encephalitis predominantly affects young women with acute or subacute onset. Clinical manifestations primarily include psychiatric and behavioral abnormalities, seizures, memory deficits, decreased consciousness, movement disorders, autonomic dysfunction, central hypoventilation, and cognitive impairment. Seizures can occur at any stage of the disease course [3]. However, the relationship between OT and anti-NMDAR encephalitis and its pathogenesis remain unclear. Patients often initially present to neurology departments with neurological and psychiatric symptoms, leading to frequent misdiagnosis or delayed diagnosis. Diagnosis is confirmed through positive anti-NMDAR antibody testing accompanied by detection of OT, after which patients are transferred to gynecology for surgical treatment. Delayed treatment and severe complications can be life-threatening, while early tumor resection significantly improves neuropsychiatric symptoms and reduces recurrence. This review summarizes research progress on the pathogenesis, diagnostic methods, and treatment strategies of OT-associated anti-NMDAR encephalitis

to enhance gynecologists' understanding of this disease and provide new directions for clinical management.

1. Literature Search Strategy

English databases (PubMed, Medline, Web of Science) were searched using the keywords "ovarian teratoma," "Anti-N-methyl-D-aspartate receptor encephalitis," "anti-NMDAR antibody encephalitis," "NMDAR," and "pathogenesis." Chinese databases (CNKI, Wanfang, VIP) were searched using the Chinese equivalents. The search timeframe spanned from database inception to February 2023. Inclusion criteria comprised clinical studies, basic research, and literature reviews on ovarian teratoma-associated anti-NMDAR encephalitis. Exclusion criteria included irrelevant topics, unavailable full texts, poor quality, outdated publications, and duplicate studies.

2. NMDAR Structure and Function

NMDAR belongs to the ionotropic glutamate receptor family and forms a heterotetramer composed of NR1, NR2, and NR3 subunits. NR1 is the essential functional subunit with ligand-binding activity, containing a glycine binding site that is necessary for ion channel function and plays a decisive role in receptor activation [4]. NR2 is a regulatory subunit containing glutamate binding sites that determine NMDAR agonist affinity, Ca^{2+} permeability, and Mg^{2+} sensitivity [5]. NR2 subtypes (NR2A, NR2B, NR2C, NR2D) combine with NR1 to form NMDARs with distinct functions and brain distributions. NR3 (including NR3A and NR3B) is also a regulatory subunit with glycine binding sites that negatively modulates Ca^{2+} permeability and Mg^{2+} sensitivity, conferring neuroprotective effects [6].

NMDARs are widely distributed in the brain and spinal cord, with different subtypes showing regional variations. NR2A is highly expressed in the adult hippocampus and cerebral cortex, while NR2B is highly expressed in the striatum [7]. Functional NMDARs typically consist of two NR1 and two NR2 subunits, though some contain two NR1, one NR2, and one NR3 subunit.

NMDAR channel opening is controlled by both ligand binding and membrane potential. In addition to neuronal depolarization, NMDAR activation requires simultaneous binding of glycine to NR1 and glutamate to NR2 [8]. At resting potential, voltage-dependent Mg^{2+} block inhibits postsynaptic NMDAR function. When excitatory impulses arrive, presynaptic release of glutamate and glycine generates excitatory postsynaptic potentials that relieve Mg^{2+} blockade, allowing channel opening, massive Ca^{2+} influx, and activation of long-term potentiation. This process participates in synaptic remodeling, memory encoding, and learning/memory maintenance. Consequently, NMDAR dysfunction causes various psychiatric and neurological symptoms.

3. Pathogenesis of OT-Associated Anti-NMDAR Encephalitis

The prevailing theory posits that OT produces anti-NMDAR antibodies that cross the blood-cerebrospinal fluid barrier (BCSFB) and mediate neuronal injury [9]. The process involves: (1) OT containing apoptotic tumor cells, glial cells, inflammatory cells, and tertiary lymphoid structures with germinal centers; (2) Mature dendritic cells capture NMDAR antigens released by apoptotic tumor cells and present antigen fragments to $CD4^+$ T cells via MHC class II complexes, inducing T cell activation, differentiation, and proliferation. Activated $CD4^+$ T cells then induce B cell differentiation into plasma cells producing large quantities of IgG autoantibodies. These immune cells and autoantibodies circulate through blood and lymphatic systems, crossing the BCSFB into cerebrospinal fluid; (3) Autoantibodies primarily target the hippocampus and prefrontal cortex, binding to epitope regions in the amino-terminal domain of the NR1 subunit, inducing NMDAR cross-linking, disrupting interactions with synaptic proteins such as Ephrin-B2 receptor, and ultimately causing NMDAR internalization and degradation, thereby reducing synaptic and extrasynaptic NMDAR numbers.

3.1 Heterotypic Neurons and Immune Cells in OT Tissue OT tissues contain glial tissue, lymphocyte aggregates, and megakaryocytic heterotypic neurons. Day et al. [10] identified heterotypic neurons with ganglioglioma and ganglioneuroblastoma-like changes in tumor tissues from OT-associated anti-NMDAR encephalitis patients. Nolan et al. [11] reported colocalization of glial tissue and lymphoid aggregates with germinal centers in tumor tissues, with abundant astrocyte populations within nerve fibers but no mature neurons. While mature neurons exhibit well-developed dendritic morphology and co-express microtubule-associated protein 2 (MAP2) and neuronal nuclear antigen (NeuN), tumor tissues from OT-associated anti-NMDAR encephalitis patients contain small cells with short stalk-like processes showing an $MAP2^+/NeuN^-$ immunophenotype, possibly representing damaged or degenerating neurons. Jiang et al. [12] made similar observations, finding aggregates of heterotypic neurons with irregular shapes, giant nuclei, and floating frog-like appearances exclusively in OT tissues from anti-NMDAR encephalitis patients. These neurons showed strong immunoreactivity for NMDAR subunits NR1, NR2A, and NR2B, with immunofluorescence demonstrating colocalization of NMDAR subunits with IgG, suggesting that autoantigens may originate from heterotypic neurons and trigger anti-NMDAR encephalitis. Chefdeville et al. [13] also found that OT tissues from anti-NMDAR encephalitis patients contained more glial components and immune cells, including T cells, B cells, and mature dendritic cells, consistent with tertiary lymphoid structures. These immune cells showed persistent infiltration of neural tissue components, with IgG, IgA, and plasma cells in close contact with glial tissue, suggesting involvement in triggering or maintaining immune responses. Makuch et al. [14] extracted B cells from tumor tissues of OT-associated anti-NMDAR encephalitis patients and cultured them in vitro to produce NR1-specific IgG, confirming the link between OT-associated anti-

NMDAR encephalitis and humoral immune-mediated autoimmunity. It is hypothesized that heterotypic neurons within tumor tissues express autoantigens that induce humoral immune responses, with corresponding antibodies to NR1 and NR2 subunits present in germinal centers of lymphoid aggregates. Glial tissue also participates in triggering and maintaining immune responses, causing persistent autoimmune neuronal injury and leading to mature neuron loss and neurological dysfunction symptoms.

3.2 Anti-NMDAR Antibody Translocation Across the BCSFB Patient immune cells produce autoantibodies that cross the BCSFB into cerebrospinal fluid to mediate neuronal injury and cause corresponding symptoms, though the mechanism of antibody translocation remains unclear. Hammer et al. [15] extracted anti-NMDAR antibodies from patient sera and injected them into mouse tail veins. While intact BCSFB in healthy wild-type mice effectively prevented antibody entry into the hippocampus, $APOE^{-}/^{-}$ mice with BCSFB defects showed reduced spontaneous activity. The albumin quotient (QAlb), the ratio of cerebrospinal fluid albumin to serum albumin, serves as a BCSFB function indicator, with Qlim(Alb) calculated as 4 + (age/15). BCSFB dysfunction is defined as QAlb > Qlim(Alb). Wang et al. [16] found that 29.3% of anti-NMDAR encephalitis patients had QAlb > Qlim(Alb), indicating BCSFB dysfunction. Yu et al. [17] demonstrated that increased intrathecal IgG synthesis correlated significantly with QAlb changes, with greater BCSFB damage enhancing endogenous central nervous system immune responses. OT-associated anti-NMDAR encephalitis patients often show elevated tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10), and granulocyte-macrophage colony-stimulating factor (GM-CSF) levels [12]. TNF-α regulates BCSFB permeability through internalization of tight junction proteins in endothelial cells, while GM-CSF upregulates pro-inflammatory cytokines produced by macrophages or dendritic cells and promotes differentiation of hematopoietic progenitors into myeloid cells, disrupting the BCSFB and facilitating serum antibody transfer to cerebrospinal fluid. Patients frequently have autonomic dysfunction manifesting as hypertension and sympathetic hyperactivity, which increases BCSFB permeability [18]. The BCSFB is closely associated with OT-related anti-NMDAR encephalitis, suggesting that immune responses and inflammatory infiltration disrupt BCSFB integrity, leading to dysfunction that allows anti-NMDAR antibodies to cross the barrier.

3.3 Squamous Epithelial Tissue in OT NMDAR is highly expressed on the cell membranes of epidermal keratinocytes and plays an important role in maintaining skin barrier stability. OT tissues typically originate from three germ layers: ectoderm, mesoderm, and endoderm. Neural tissue, hair, and skin appendages all derive from the ectoderm, sharing common embryological receptors. NMDAR expression in squamous epithelial tissue may contribute to anti-NMDAR encephalitis development. Lark et al. [19] noted that in OT-associated anti-NMDAR encephalitis patients whose tumor tissues lack neural components,

squamous tissue is the only site expressing NMDAR. Xiao et al. [20] similarly found high NR1 subunit expression in squamous cell tissues near glial cells and lymphocyte infiltration. Jiang et al. [21] also reported positive NMDAR subunit staining in sebaceous glands and squamous tissues of OT, in addition to neural tissue. However, due to the lack of specific serum tumor markers, some studies suggest that elevated serum CA125, CA199, and AFP levels may assist in OT diagnosis [25-27]. Since OT lacks specific clinical manifestations, OT-associated anti-NMDAR encephalitis patients typically present only with anti-NMDAR encephalitis-related symptoms. Diagnosis is often delayed as OT is only detected through imaging after confirming anti-NMDAR encephalitis via typical clinical presentation, cerebrospinal fluid analysis, electroencephalography, and antibody testing. Therefore, young women presenting with anti-NMDAR encephalitis manifestations should immediately undergo ovarian tumor screening to enable early collaborative diagnosis and treatment between gynecology and neurology.

3.4 Genetics of OT-Associated Anti-NMDAR Encephalitis Zhao et al. [22] demonstrated significantly elevated HLA-A and HLA-DRB1 levels in tumor tissues from OT-associated anti-NMDAR encephalitis patients, suggesting that some autoantigen in OT tissues causes increased HLA-A and HLA-DRB1 proteins. The resulting autoantibodies may attack the central nervous system through the BCSFB, though no direct evidence currently supports this hypothesis. Xiao et al. [20] made similar observations, with more pronounced HLA-A^+ and HLA-$DRB1^+$ cell aggregates. These alleles are associated with increased susceptibility to various autoimmune diseases, but their specific association with OT-associated anti-NMDAR encephalitis susceptibility remains unclear and requires further investigation.

4. Clinical Manifestations

4.1 Clinical Manifestations of Anti-NMDAR Encephalitis The disease presents acutely or subacutely, with prodromal symptoms including fever, headache, and nausea. Typical symptoms emerge within 2 weeks to several months, manifesting as psychiatric and behavioral abnormalities, seizures, memory deficits, decreased consciousness, movement disorders, cognitive impairment, speech disorders, autonomic dysfunction, central hypoventilation, and orofacial dyskinesia. Psychiatric and behavioral abnormalities are the initial manifestation in 60.9% of anti-NMDAR encephalitis patients with OT, including anxiety, delusions, mania, and catatonia [23]. Patients often have sleep disturbances and focal central nervous system damage, presenting as insomnia, hypersomnia, excessive daytime sleepiness, sleep-wake cycle disorders, diplopia, ataxia, and hemiplegia.

4.2 Clinical Manifestations of OT OT lacks specific manifestations and is often discovered incidentally on imaging. Most are unilateral. Large tumors

may cause abdominal pain, palpable masses, and abdominal distension. Complications such as torsion, rupture, and infection may occur, with torsion being most common, presenting as sudden severe unilateral lower abdominal pain with nausea and vomiting; severe cases may develop shock due to peritoneal traction and strangulation. A minority of patients may experience tumor rupture causing chemical peritonitis. Due to the nonspecific clinical presentation of OT, OT-associated anti-NMDAR encephalitis patients often first visit neurology departments with neurological and psychiatric symptoms, leading to misdiagnosis or missed diagnosis that requires further investigation for confirmation before transfer to gynecology for surgical treatment.

In 2016, Graus et al. [24] proposed diagnostic criteria for anti-NMDAR encephalitis in *Lancet Neurology*, divided into probable and definite diagnoses. The main criterion for definite diagnosis is clinical symptoms plus positive anti-NMDAR antibodies . Ultrasound is the first-line imaging modality for OT screening, with CT or MRI used when ultrasound is inconclusive.

6. Treatment

6.1 Surgical Treatment Early tumor resection in OT-associated anti-NMDAR encephalitis patients significantly improves prognosis and reduces encephalitis recurrence. Severe systemic and neurological complications should not be considered contraindications for surgery [28]. If OT persists long-term, continuous antigen presentation induces generation of long-lived plasma cells and increases antibody affinity, rendering later tumor removal and immunotherapy ineffective. For patients without detectable OT, prophylactic oophorectomy is not recommended. Masghati et al. [29] reported identical twin patients where pelvic ultrasound, CT, and MRI revealed no ovarian lesions and immunotherapy was ineffective. One patient continued immunosuppressive therapy and ultimately died; autopsy found no OT. The other underwent bilateral salpingo-oophorectomy, with pathology showing no ovarian or tubal abnormalities; postoperative immunotherapy led to gradual recovery. This suggests that ovaries may contain microscopic teratomas undetectable by imaging, recommending oophorectomy for refractory anti-NMDAR encephalitis patients with poor immunotherapy response. Patients with postoperative pathology showing immature ovarian teratoma require additional oncological treatment such as chemotherapy beyond surgery and immunotherapy. For pregnant patients, case reports demonstrate that surgical OT removal combined with first-line immunotherapy effectively alleviates clinical symptoms and accelerates recovery after delivery or pregnancy termination [30]. Ovarian tumor resection during pregnancy does not increase fetal malformation or stillbirth risk; laparoscopic surgery is preferred with adequate perioperative management. For mid-trimester patients, if immunotherapy effectively controls symptoms, maintenance therapy may continue until the third trimester; if disease progresses, surgical OT removal or cesarean section may be necessary for better pregnancy outcomes [31].

6.2 Immunotherapy Surgery combined with immunotherapy provides faster symptom relief, shorter treatment duration, and reduced severe neurological complications [32]. Immunotherapy includes first-line, second-line, and third-line regimens, with drugs, indications, mechanisms, and complications summarized in [33-34]. First-line therapy comprises corticosteroids, intravenous immunoglobulin, and plasma exchange; second-line includes rituximab, cyclophosphamide, mycophenolate mofetil, and azathioprine. Some pregnant patients who fail first-line therapy respond to second-line agents, but cyclophosphamide and rituximab should be avoided during viable pregnancy due to teratogenicity and preterm labor risks [30]. Third-line therapies include bortezomib, tocilizumab, and anakinra.

7. Prognosis of OT-Associated Anti-NMDAR Encephalitis

Approximately 80% of OT-associated anti-NMDAR encephalitis patients achieve complete recovery or have only mild sequelae. Irritability is the most common and persistent psychiatric symptom. A minority of cases have severe disability or death, usually associated with refractory status epilepticus, severe complications, immature teratoma pathology, or treatment delay [9]. A domestic single-center prospective study showed that within one year of treatment, 94.1% of patients improved, 2.3% died, and 17.3% relapsed [35]. Higher serum and cerebrospinal fluid anti-NMDAR antibody titers correlate with worse prognosis. Most patients experience first relapse within 2 years of initial treatment, though cases of first relapse after 6 years have been reported, necessitating long-term follow-up. Early OT resection combined with immunotherapy reduces recurrence risk and significantly improves long-term prognosis, preventing more severe neurodegeneration.

8. Other Gynecological Tumors Associated with Anti-NMDAR Encephalitis

In addition to OT, anti-NMDAR encephalitis is associated with various tumors including small cell lung cancer, esophageal cancer, breast cancer, and thymic cancer. Gynecology-related tumors include ovarian cancer [28], ovarian mucinous cystadenoma [36], and ovarian cystadenofibroma [37]. Patients with ovarian mucinous cystadenoma and cystadenofibroma who underwent unilateral salpingo-oophorectomy and immunotherapy all recovered well without recurrence. Currently, only ovarian tumors have been found to co-occur with anti-NMDAR encephalitis; the association and pathogenesis with other female genital organs such as the cervix, uterine corpus, and fallopian tubes remain to be further investigated.

9. Summary and Outlook

OT-associated anti-NMDAR encephalitis lacks specific early diagnostic biomarkers, making it prone to missed diagnosis and delayed treatment. Young women

presenting with psychiatric symptoms or seizures should be evaluated for anti-NMDAR encephalitis, with prompt tumor screening and serum/cerebrospinal fluid anti-NMDAR antibody testing. Early OT resection combined with immunotherapy improves prognosis after diagnosis. Further exploration of the molecular mechanisms of OT-associated anti-NMDAR encephalitis and development of more effective drugs and novel therapies will be key to improving clinical outcomes.

Author Contributions: ZHANG Shan conceived the research, retrieved literature, collected data, and drafted the manuscript; ZHANG Meng collected literature and revised the manuscript; XU Xin and LIAO Lixin retrieved and organized literature; SUN Mingjun and MA Haiyan revised the manuscript; ZHANG Haibin and GUO Yuzhen supervised and oversaw the entire project.

Conflict of Interest: None declared.

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Table 1 Diagnostic Criteria for Anti-NMDAR Encephalitis

Probable Anti-NMDAR Encephalitis

Meets all three criteria:

1. Rapid onset (course <3 months) with at least 4 of 6 main symptoms (only 3 required if teratoma present):

Psychiatric/behavioral abnormalities or cognitive impairment

Speech disorder: continuous, uninterruptible forced speech, reduced speech, or mutism

Seizures

Movement disorders, dyskinesias, or rigidity/abnormal posturing

Decreased level of consciousness

Autonomic dysfunction or central hypoventilation

2. At least one abnormal ancillary test:

Abnormal EEG: focal or diffuse slowing/rhythmic disturbance, epileptiform discharges, or extreme delta brush

CSF pleocytosis or oligoclonal bands

3. Reasonable exclusion of other diseases: herpes simplex encephalitis, glioma, status epilepticus, neurosyphilis, Whipple's disease, AIDS, etc.

Definite Anti-NMDAR Encephalitis
Meets all three criteria:
1. Rapid onset (course <3 months) with at least 4 of 6 main symptoms (only 3 required if teratoma present)
2. Positive anti-NMDAR IgG antibodies in CSF or serum
3. Reasonable exclusion of other etiologies, such as recent herpes simplex virus encephalitis or Japanese encephalitis

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Table 2 Immunotherapy for OT-Associated Anti-NMDAR Encephalitis

Category	Agent	Indications	Mechanism	Complications
First-line	Corticosteroids	First choice; IV superior to oral; methylprednisolone pulse preferred	Bind intracellular glucocorticoid receptors; inhibit transcription of inflammatory genes (cytokines, chemokines); affect anti-inflammatory protein synthesis; reduce T cell circulation and Th1 differentiation; restore BBB integrity	Hypertension, hyperglycemia, hemorrhage, weight gain, Cushing's syndrome, reactive leukocytosis, infection risk, osteoporosis, delayed wound healing, avascular necrosis

Category	Agent	Indications	Mechanism	Complications
	Intravenous Immunoglobulin	IV use combined with corticosteroids for severe/refractory cases	Neutralize autoantibodies; affect complement system via immune complex clearance; inhibit B cell proliferation/antigen presentation; modulate regulatory T cells	Influenza-like symptoms, skin allergy (urticaria, eczema, maculopapular rash), arrhythmia, hypotension, headache, renal impairment, thrombosis, neutropenia, pulmonary edema
	Plasma Exchange	Used when corticosteroids contraindicated or ineffective; unsuitable for agitated/uncooperative patients	Remove autoantibodies, cytokines, and immune complexes; enhance macrophage/monocyte function; increase antibody-producing cell sensitivity to immunosuppressants	Catheter-related infection/complications, hypotension, electrolyte imbalance, paresthesia, muscle cramps, hypocalcemia, pruritus, urticaria
Second-line	Rituximab	Patients receiving rituximab after first-line or combined with first-line show better outcomes than first-line alone	Antibody-mediated cytotoxicity via complement activation and apoptosis; depletes naive and memory $CD20^+$ B cells	Infusion reactions, infection risk, body aches, nausea, fatigue, cytopenias, hypogammaglobulinemia

Category	Agent	Indications	Mechanism	Complications
	Cyclophosphamide	Used for refractory/severe cases after first-line; caution in myelosuppression, hemorrhagic cystitis, bladder cancer, infertility	Alkylating agent inhibiting cell proliferation; suppresses cellular and humoral immunity via effects on T and B cells	Myelosuppression, infection, nausea, vomiting, alopecia, agranulocytosis, infertility, hemorrhagic cystitis
	Mycophenolate Mofetil	Recurrence, poor first-line response, or tumor-negative patients	Purine metabolism inhibitor acting mainly on lymphocytes	GI symptoms, hypertension, edema, myelosuppression, infection
	Azathioprine	Recurrence, poor first-line response, or tumor-negative patients	Purine synthesis antagonist inhibiting DNA, RNA, and protein synthesis	Fever, myalgia, GI symptoms, rash, infection, hypersensitivity, cytopenias, myelosuppression, elevated liver enzymes
Third-line	Bortezomib	Poor BBB penetration; currently for resistance to other second-line drugs	Selective proteasome inhibitor reducing plasma cell generation	Infection risk, fever, GI symptoms, headache, dizziness, paresthesia, cytopenias, hypotension, dyspnea, shingles, peripheral neuropathy

Category	Agent	Indications	Mechanism	Complications
	Tocilizumab	Rituximab-resistant patients	Recombinant IL-6 receptor antagonist blocking IL-6-mediated inflammatory cascade	Infection risk, fever, GI symptoms, headache, dizziness, paresthesia, cytopenias, hypotension, dyspnea, shingles, peripheral neuropathy
	Anakinra	Reduces seizure frequency and duration	Recombinant IL-1 receptor antagonist	Infection risk, fever, blunted CRP response, neutropenia, thrombocytopenia, elevated liver enzymes, hyperlipidemia, headache, GI symptoms, neutropenia, URI, injection site reactions, urticaria, serious infections

IL = interleukin

Note: Figure translations are in progress. See original paper for figures.