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Diagnosis and management of adult central nervous system leukemia

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Abstract

Central nervous system leukemia (CNSL) is a prominent infiltration reason for therapy failing in acute leukemia. Recurrence rates and the prognosis have alleviated with current prophylactic regimens. However, the accurate stratification of relapse risk and treatment regimens for relapsed or refractory patients remain clinical challenges yet to be solved. Recently, with hematopoietic stem cell transplantation (HSCT) and chimeric antigen receptor-T (CAR-T) cellular therapy showing encouraging effects in some CNSL patients, advances in treating CNSL have already been reported. The development of molecular targeted agents as well as antibody-based drugs will provide patients with more personalized treatment. This article summarized recent research developments about risk factors, diagnosis, prevention, and treatment in adults with CNSL.

Key Words: Central nervous system leukemia; Prophylaxis; Risk factors; Treatment

1. INTRODUCTION

Central nervous system leukemia (CNSL) is extramedullary leukemia resulting from leukemic cells invading the meninges, cerebral nerves, brain tissue, and spinal cord. Chemotherapeutic drugs are prevented from accessing the central nervous system (CNS) by the blood–brain barrier (BBB), causing the CNS a refuge for leukemia cells and the common site for extramedullary leukemia relapse. Adult CNSL incidence is low, with less than 10% of patients initially diagnosed with CNS involvement (CNSi),[1–3] but the value could be as high as 75% after 1 year if active prevention was not implemented.[4] Adult acute lymphoblastic leukemia (ALL) has a higher CNSi rate and a worse prognosis than acute myeloid leukemia (AML), with an average survival time of 6 months.[4] Allo-HSCT is the only cure available today. By comparison, the CNSi in chronic myeloid leukemia (CML) and chronic lymphoblastic leukemia (CLL) is rare and few cases are reported.[5–9] Overall, early diagnosis, prevention, and treatment of CNSL are necessary. Conventional CNS prophylactic regimens have lowered the prevalence of CNS disease significantly,[4,10,11] but some patients with relapsed or refractory (R/R) CNSi demand more robust and targeted therapeutic options to improve outcomes. Due to a deeper comprehension of the pathogenesis, additional therapeutic possibilities such as HSCT, CAR-T cellular therapy, molecular targeted agents, and antibody-based drugs have been reported to have potential efficacy in leukemia patients with CNSi. This article reviewed the most recent progress in adult CNSL risk factors, diagnosis, prevention, and therapy during the past 5 years.

2. RISK FACTORS

Common risk factors associated with CNS in adults include WBC > 50×10^9/L at diagnosis, T-cell phenotype, presence of a mediastinal mass, high lactate dehydrogenase (LDH) levels, high proliferation index, and the existence of leukemic cells in the cerebrospinal fluid (CSF).[2,12–14] Furthermore, some high-risk cytogenetic characteristics, such as KMT2A rearrangements, Philadelphia chromosome (Ph) positive, and a mature B-cell immunophenotype, are independent risk features for CNS disease development.[14,15] CNSi is relatively rare in AML patients, and the patients with the M4, M5, 11q23 abnormalities, inv(16), or nuclear phosphoprotein 1 (NPM1) mutations are thought to be at increased risk.[3,16] According to Cheng et al,[3] inv(16) is more frequent in patients with early CNS illness, while 11q23 abnormalities are more prevalent in those with isolated CNS relapses. The pathogenic variation p.L387M and heterozygotes for the NBN gene c.657_661del5 mutation seem to have a greater probability of CNS recurrence.[15,17] Polymorphisms in genes encoding proteins associated with anti-leukemic drug pharmacodynamics (vitamin D receptor locus, highly active thymidylate synthase 3/3 genotype) are also linked to increased CNSi, implying the reason may be related to the function of p-glycoprotein and methotrexate (MTX) resistance.[12,18] CD56 expression and higher lncRNATUG1 levels have also been identified as dangerous causes for CNSi in adults.[19,20]

WBC, LDH, vascular endothelial growth factor (VEGF), β_2-microglobulin and albumin (ALB) levels in CSF can be used

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to evaluate BBB status, which is a key event in tumor metastasis. Munch et al[21] discovered noticeably increased amounts of VEGF protein in CSF samples of acute leukemia patients with CNSi. Bergstrom et al[22] observed a connection between leukocyte immunoglobulin-like receptor B4 (LILRB4) and CNSi in AML patients. Strati et al stated[23] that low glucose levels in CSF, elevated nucleated cell counts and lymphocyte counts were associated with CNSi in CLL patients. However, the researchers also noted that despite statistical differences in these characteristics, there are not enough reliable clinical data to identify whether CLL is to blame for CNSi or other factors.[23] Regardless, these studies imply that using circulating biomarkers to monitor the incidence of CNSL may be advantageous for patient management.

3. DIAGNOSIS

There are no standard CNSL diagnosis criteria. It is generally considered that a CSF leukocyte count $\geqq 0.005 \times 10^9$/L and centrifuged specimens demonstrating primitive cells can be diagnosed. CNSL can manifest as soft meningitis or, rarely, as a solid mass.[14] Currently, CNSL is mainly diagnosed by clinical symptoms, imaging, and CSF investigation.

The tumor burden and anatomical site of leukemic cell infiltration affect how CNSL presents clinically. It might manifest as sensory or motor deficits, cognitive-behavioral abnormalities, headache, vomiting, or other signs.[23–27] Since the CNSi is less in CML and CLL patients, clinicians should pay closer attention to the CNS symptoms of these patients to make a correct diagnosis (Table 1). However, CNS symptoms alone cannot identify CNSL, as demonstrated by a trial including 103 adult patients who were newly diagnosed with AML. In this trial recruited participants had regular lumbar puncture (LP) screening, and more than 90% (30/32) of patients with CNSi lacked any CNS signs or indicators.[28] Rozovski et al[29] analyzed the patient files of 1412 AML patients and discovered that only 3.3% of 1370 patients with established clinical signs had CNSi. Instead, CNS illness was found in 8 (19%) of the remaining 42 patients who had LP as a condition for participation in the trial.

Conventional cytology (CC) is a common diagnostic method, with false negative rates as high as 41% sometimes.[30] Flow cytometry (FCM) and polymerase chain reaction (PCR) have increased the sensitivity of assays.[1,28,31] Garcia et al[31] tested 92 patients with ALL by FCM and CC, finding 18 positives for FCM and 6 positives for CC. The cumulative recurrence rate of CNS in FCM+ patients was substantially greater than in FCM– patients (22% vs 5%, P = .044). While there was no such relationship between CC results and CNS recurrence, suggesting that CSF FCM may be superior to CC in identifying people at high risk of CNS recurrence. Gong et al[13] detected 357 adult ALL patients using FCM and CC. The 2-year overall survival (OS) rates in the FCM+/CC– and FCM+/CC+ groups were 40.0% and 20.6% respectively, with no significant statistical difference (P = .195). The findings demonstrated the clinical importance of a single FCM+ status, supporting that FCM has better sensitivity than CC in identifying the CNSi aspect. But, as FCM is complicated and requires expertise in handling, processing, and analyzing samples, it cannot replace CC completely. Combining CC with FCM to enhance diagnosis accuracy is recommended, particularly in patients with minor disease burdens. Immunocytochemistry (IC), which tests leukemia-associated cell surface antigens, has also been utilized for diagnosis. In hematologic malignancies, Zeiser and colleagues[32] found extraordinarily high sensitivity (89%–95%) by IC. Timmers et al[6] proposed that CLL patients with CNSi should undergo CSF immunophenotyping to compensate for false negatives on imaging and CC.

Computed tomography (CT) and magnetic resonance imaging (MRI) are 2 imaging methods often used to diagnose CNSi. CT is useful for identifying bigger tumors while MRI is more sensitive in minor lesions or soft meningeal abnormities, which is a typical site of leukemic cell infiltration.[14] Shen et al[33] reported that the sensitivity of MRI for identifying CNSi in AML patients is 36.90%. Imaging may be possible to reveal mass lesions in the brain in patients with clinical symptoms but a negative CSF test (although less common), and this situation often requires more active therapies.

4. PREVENTION AND TREATMENT

Most ALL patients get regular CNS prophylaxis. Without prevention, the incidence of CNSL can be as high as 75% after 1 year.[4] With current prevention programs, this figure has been reduced to about 4%.[10,11,34] This demonstrates the benefit of timely prevention and optimal management of primary diseases in reducing CNSi. In contrast, AML patients are less inclined to develop CNSi[3] and the National Comprehensive Cancer Network (NCCN) suggests that LP be avoided in patients who do not have CNS symptoms at first diagnosis. However, the frequency of CNSi in AML patients may be higher than expected. Rozovski et al[29] noted that if LP were conducted on all AML

Table 1

Different CNS symptom of CNSL.

CNS doman	CNS symptom	Leukemia type	References
Cerebral	Altered mental status	CLL, ALL, AML	6,7,25,27
	Cerebrovascular complications	ALL	25
	Headache	CLL, CML, ALL, AML	3,5,8,9,21,25,27
	Dizziness	AML	3
	Nausea and vomiting	CLL, CML	5,9
	Seizure	CLL, ALL, AML	3,5,25,27
	Gait disorder	CLL	8,21
Cranial nerves	Diplopia	CLL, ALL	6,22
	Optic perineuritis	CLL	23
	Sensory deafness	CML	24
	Visual loss	CLL, CML, ALL, AML	3,6,9,25
	Dysphagia	CLL	8
	Facial nerve paralysis	CLL, ALL, AML	8,22,27
Spinal	Paresthesia	CLL, ALL, AML	3,21,25,27
	Back pain	ALL	22

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, CLL = chronic lymphoblastic leukemia, CNS = central nervous system, CNSL = central nervous system leukemia, CML = chronic myeloid leukemia.

patients when diagnosing, the rate of CNS disease would reach 20%. Furthermore, adult AML patients have a dismal outcome, with just 6% of patients over 65 years old surviving 2 years after diagnosis.[35] More prospective trials are necessary to determine if CNS prophylaxis should be included as part of AML induction therapy.

4.1. Systemic chemotherapy

Keeping medication concentrations in the CSF during chemotherapy is crucial for avoiding CNSi, and medicines often used include MTX, cytarabine (Ara-C), and steroid.

High-dose MTX and Ara-C can cross the BBB and are useful in CNS prophylaxis. But increasing the dose, on the other hand, raises the risk of drug toxicity. Mateos et al[36] carried out a systematic review study of 1251 Australian children, finding that 7.6% had MTX neurotoxicity. Patients with elevated levels of serum aspartate aminotransferase or age over 10 when diagnosed are more likely to appear with MTX neurotoxicity. A study described the use of ultrasound in conjunction with microbubble-loaded Ara-C to open the BBB reversibly and locally, hence enhancing Ara-C BBB penetration.[37] In this way, a normal dose of Ara-C can produce a similar efficacy to large doses while avoiding the severe toxic side effects due to high doses. This novel method of medication administration brings up new possibilities for treating CNSL. Steroid hormones have been widely employed in CNS prevention. Dexamethasone (DEX) is more permeable in CSF than prednisone, has a longer half-life, and is more effective in lowering the risk of CNSL.[38–40]

In addition, asparaginase, thiopurines, and other drugs are employed in chemotherapy regimens to provide efficient CNS prophylaxis and have decreased CNS recurrence rates even further. One of the most commonly utilized therapy regimens for ALL adults is Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and DEX alternating with MTX and Ara-C).[4] Researchers altered 4 rounds of Hyper-CVAD plus HD MTX and Ara-C in ALL adult patients, adding intrathecal injection (IT) MTX and IT Ara-C as needed. They found that 91% of patients had reached complete remission (CR), with only 4% suffering CNS recurrence.[10] Conversely, Garcia et al[31] observed less encouraging results with Hyper-CVAD treatment. Researchers discovered that individuals initially diagnosed as positive CSF had cumulative CNS recurrence rates up to 22% despite having had at least 4 cycles of Hyper-CVAD treatment.

4.2. Intrathecal injection

IT chemotherapy plays an integral role in CNS prevention by allowing direct injection from the CSF, thus maintaining the therapeutic concentrations of medication. The mixture of IT treatment and timely, aggressive systemic chemotherapy reduced the possibility of CNS recurrence to 4% in ALL patients.[4] Commonly used IT agents include DEX, MTX, and Ara-C, in 2 or 3 combinations. Dara et al[41] employed front-line IT chemotherapy with MTX 15 mg and DEX 4 mg in patients with CNSi and malignant hematologic illness, achieving CSF CR in 76% of patients. When paired with second-line IT therapy with Ara-C 70 mg and DEX 4 mg, CSF CR was obtained in 91% of patients. Despite the remarkable remission rate, CNS relapses followed in 38% of patients. Notably, CNS recurrence occurred in 50% of patients with diffuse large B-cell lymphoma (DLBCL) and primary central nervous system lymphoma (PCNSL) but in 14% of leukemia patients (ALL and AML). Moreover, the quantity and time of IT should be carefully considered. Paul et al[42] examined the CNS recurrence rate in Ph^+ individuals who received >8 IT and <8 IT prophylaxis. The results showed that patients who received >8 IT had a lower CNS relapse rate (0% vs 10%, $P = .023$) and a higher 3-year CNS disease-free survival (DFS) (100% vs 92%, $P = .06$) during the follow-up period. Alternatively, the case of IT MTX-induced myelopathy was also recorded.[43] Ara-C can be given encapsulated in liposomes, which can keep medication therapeutic quantities in the CSF for up to 2 weeks. Nonetheless, the impact of increasing toxicity should not be underestimated.[44,45] In a study by Bassan et al,[45] 17 patients (24%) in the lipid Ara-C group experienced grade 3–4 neurotoxicity, while such patients were only 2 (3%) in the triple therapy group. Conversely, other studies demonstrated the safety of liposomal Ara-C.[46,47] In a retrospective study, McClune and colleagues[46] found that the administration of liposome Ara-C once per cycle in Hyper-CVAD was well tolerated by patients. More research is required to figure out the optimum dose strategy for this highly potent drug while minimizing its toxicity.

4.3. Radiotherapy

Although radiation has shown efficacy in CNS prophylaxis, its usage has been limited because of serious side effects such as secondary malignancies and neurocognitive deficits. Previously, many trials have proved the validity of CNS prophylactic techniques without cranial irradiation.[48,49] It is now generally accepted that radiation should be ignored in low-risk groups, and even in high-risk populations, radiotherapy doses should be carefully provided to avoid unmanageable toxic side effects. According to recent studies, pretreatment of patients with craniospinal irradiation before HSCT decreased the likelihood of CNS recurrence after transplantation,[50] while further research is necessary to evaluate the benefit of this regimen.

4.4. Hematopoietic stem cell transplantation

In recent years, HSCT has proven successful in the therapy of CNSL, improving the outcomes in patients with CNSL.[51] Chiba et al[26] proposed that allo-HSCT would prolong life in CNS-CML patients. After reviewing 22 prior cases, the results revealed that 2 patients receiving allo-HSCT after CNSi survived, while 10 of 20 patients who did not undergo allo-HSCT died.

Notably, extramedullary recurrence still exists even after transplantation,[52] and the prognosis for individuals experiencing post-transplant CNS disease is dismal. In the research by Bharucha et al,[53] none of the 7 patients with CNS recurrence after transplantation lived after 3 years. A history of pre-HSCT CNSi and negative cytogenetics such as inv (16) and 11q23 abnormalities are linked to a higher risk of extramedullary recurrence after HSCT.[3,52] CNS recurrence following HSCT is still challenging to avoid and manage. Enhanced graft-versus-leukemia (GVL) impact may be a better and safer way to reduce CNS relapse than nonspecific CNS prophylaxis.[54] Although there has been a study on intrathecal donor lymphocyte infusion (IDLI) for CNSi following HSCT, this approach remains in the experimental stage.[55]

It is widely accepted that patients with CNSi should be pretreated by total body irradiation (TBI) before transplantation. Kozak et al[56] examined the outcome of 116 patients who received TBI before allo-HSCT. They found that only 7 patients (3%) had CNS relapse, the median period until CNS relapse was 7 months, while the median OS of patients who suffered from CNS relapse following transplantation was 19 months. Several studies suggest that cranial boost (CB) radiation may benefit people with CNS recurrence after allo-HSCT.[57,58] Su et al[58] administered a relatively low-dose CB of 6 Gy to ALL patients at high-danger status before allo-HSCT, and the 3-year CNS DFS and OS rates in this group were 94.7% and 62.7%, respectively. In contrast, the values in patients who did not get CB were 81.8% and 51.5%. Gao et al[59] classified patients into 4 categories depending on their CNS history and whether or not they had a CB radiation regimen, and all patients were administered a TBI-based pretreatment regimen. After 2 years,

the CNS+/CB+ category saw 0% CNS recurrence, compared to 21% in the CNS+/CB– category (P = .03). More research is required to assess the influence of TBI and CB pretreatment regimens on CNS relapse and survival outcomes after allo-HSCT, which might help guide the preparation strategy for CNS patients.

4.5. CAR-T cellular therapy

Present regimens are helpful in primary patients; nevertheless, more effective regimens are needed to treat patients with R/R CNSL, to enhance the outcome of these subgroups. Anti-CD19 CAR-T cellular therapy has been proven to eliminate leukemic cells from the CNS of adult B-ALL patients safely and efficiently. In the experiment, 3 patients with CNSL reached CR after receiving CAR-T infusion within 2 weeks, and their adverse effects were successfully managed with DEX and supportive care.[60] In addition, researchers also observed higher CAR-T levels in the CSF and less severe toxic responses in isolated CNS relapse patients in comparison to those who experienced both bone marrow and CNS relapses. Qi et al[61] observed the efficacy of CD19 CAR-T for R/R B-ALL patients with CNSL. The 48 included patients achieved an 87.5% overall response rate for bone marrow disease and an 85.4% remission rate for CNSL. These patients were well tolerated, with a median event-free survival (EFS) of 8.7 months and a median OS of 16 months.

Cytokine release syndrome (CRS), hemophagocytic lymphohistiocytosis (HLH), neurological toxicity, tumor lysis syndrome, and other side effects are common during CAR-T cellular therapy. Many studies are quite selective when enrolling R/R acute leukemia patients, often eliminating individuals with significant neurological symptoms. However, according to a recent study, the frequency and extent of CAR-T-induced neurotoxicity were not significantly different between patients with or without CNSi, indicating that CNSL is not an absolute contraindication to CAR-T cellular treatment.[62] Patients treated with CD28 CAR-T cells were more likely to suffer CRS and neurotoxicity than those treated with 4-1BB CAR-T cells.[62] The possibility of CRS and CAR-T cell–associated encephalopathy syndrome is increased in patients with significant tumor load.[63] Therefore, the tumor burden should be lowered before CAR-T cellular treatment. Further research is required to confirm the therapeutic impact of CAR-T cells on CNSL. However, with more types of CAR-T cells being developed, it may replace current treatments as a new customary strategy for patients with R/R ALL in the future.

4.6. Molecular targeted drug

Currently, molecular targeted drugs have shown potential in the treatment of CNSL, and many related clinical trials are underway (Table 2).

4.6.1. Kinase inhibitors BCR-ABL1–positive ALL patients have CNS recurrence possibility between 8% and 17%, with a dismal prognosis.[15] Since the development of tyrosine kinase inhibitors (TKIs), intensive chemotherapy together with TKI has been the standard for this patient group. Nonetheless, the first-generation TKI imatinib shows poor BBB penetration, and CNS recurrence occurs in up to 23% of patients with Ph$^+$ ALL after its usage.[15] Dasatinib, a second-generation TKI, has better BBB penetration.[64] Chiba et al[26] reported successful therapy for a CML patient with CNSi using dasatinib and chemotherapy followed by allo-HSCT. A phase 3 randomized clinical study compared the effectiveness of dasatinib at 30 mg/m^2 per day to imatinib at 300 mg/m^2 per day in patients with Ph$^+$ ALL.[65] The findings showed that, in the 2 groups, the 4-year accumulated probability of an isolated CNS recurrence was 2.7% and 8.4%, respectively. But, there are also cases where dasatinib was less useful.[66] Gong et al[67] used the LC-MS/MS test to analyze the serum and CSF of Ph$^+$ ALL patients using dasatinib and found that daily oral dasatinib 100 mg was hard to penetrate the CSF. They advised a larger amount of dasatinib (140 mg/d) in individuals at increased danger of CNS recurrence or requiring CNSL therapy. Besides dosage, mutations in the structural domain of BCR-ABL1 kinase are a major cause of TKI resistance.[68] Takayoshi et al[69] compared the prognosis of 289 Ph$^+$ ALL patients who had BCR-ABL1 fusion gene mutations to those who did not. Patients in the mutant group had considerably lower rates of OS and recurrence than those in the unmutated one (OS: 34% vs 68%, P < .001; relapse rate: 48% vs 18%, P < .001). The T315I mutation made the discrepancy even more obvious (OS: 29% vs 68%, P < .001; relapse rate: 54% vs 18%, P < .001).

Ponatinib, a third-generation TKI, overcomes the problem of T315I mutational resistance. The Anderson Cancer Center reported the usefulness of ponatinib in inhibiting T315I mutant clones.[70] Subsequently, He et al[71] evaluated the utility of ponatinib in treating patients with CNSL and T315I mutation. Nine patients with T315I mutation had a profound molecular response and CNS abatement at 1.5 median months after therapy. Olverembatinib, another third-generation TKI, was reported to overcome mutations including T315I.[72] Olverembatinib appears to be safer than ponatinib, with the primary adverse events being thrombocytopenia, anemia, leukopenia, and neutropenia.[72]

Ibrutinib, an oral Bruton tyrosine kinase inhibitor (BTK) inhibitor that can penetrate the BBB, is used to treat CLL and mantle cell lymphoma. To date, multiple cases have reported effective treatment using ibrutinib in patients with CNS-involved CLL.[5,73] Ibrutinib plus rituximab improved CR rates in CLL patients with CNSi as compared with FCR (fludarabine, cyclophosphamide, and rituximab) regimen.[5] In a multicenter, prospective, phase 2 study of Ibrutinib alone for R/R PCNSL and primary vitreoretinal lymphoma, 19% of patients reached CR, 33% reached partial remission (PR), and the median OS was 19.2 months.[74] Grommes et al[75] conducted a phase 1 clinical study using ibrutinib for R/R PCNSL, and 77% of patients responded clinically, with 5 patients reaching CR. Ibrutinib has also been shown to be useful as a salvage treatment for CLL patients with CNSi after allo-HSCT.[76] More data are required, however, to validate its capacity to give survival advantages for patients with hematologic malignancies and CNSi beyond existing regimens.

Sorafenib, an oral multikinase inhibitor, is taken to treat patients with AML and FMS-associated tyrosine kinase 3-internal tandem repeat (Flt3-ITD) mutations. In animal models, it was proven that sorafenib can penetrate the BBB.[77] A case reported that sorafenib coupled with chemotherapy resulted in a marked decrease in tumor size in a young CNS-AML patient.[78] Chen et al[77] carried out a multicenter, phase 2 clinical study to evaluate the effectiveness of sorafenib in conjunction with conventional treatment for patients with refractory CNSL. The findings were promising. After 8 weeks of treatment, 21 patients finally achieved CR, and 2 were in PR, with an 80.8% CR rate and an overall response rate of 88.5%. Notably, only 3 patients (13.0%) suffered a leukemic relapse during the 11.3 months of sorafenib maintenance therapy, none of which was CNS relapse.

4.6.2. BCL-2 inhibitors Venetoclax, a BH3 analog that targets the anti-apoptotic BCL2 protein, has been approved for treating CLL patients. Scherr et al[79] indicated that a triple combination of venetoclax, DEX, and TKI provided synergistic cytotoxic effects and halted leukemic development in tissue culture and primary cell xenograft models. Reda et al[80] investigated the potential utility of venetoclax in collaboration with IT for CLL patients with CNSi. And after delivery, the minimal level of venetoclax in patient CSF was 1.5 ng/mL, which was adequate to block leukemic cell proliferation. The leukemic burden of

Table 2

Current status of targeted agents ongoing clinical trials.

Drug	NCT	Conditions	Enrollment	Phase	Status
Dasatinib	NCT02883049	• B ALL • B ALL with BCR-ABL1-like features • CNS leukemia • Testicular leukemia	5937	3	Active, not recruiting
	NCT02689440	• Chronic phase CML, BCR-ABL1 positive • Ph positive, BCR-ABL1 positive CML	140	2	Recruiting
	NCT01593254	• Chronic phase CML	262	2	Completed
	NCT01310010	• ALL, Ph positive	30	2	Completed
Ponatinib	NCT05268003	• ALL • Leukemia	20	2	Recruiting
	NCT04475731	• Ph positive ALL • ALL, in relapse	67	2	Recruiting
Olverembatinib	NCT05466175	• Ph positive ALL	55	2	Not yet recruiting
	NCT05311943	• CML, chronic phase • Tyrosine kinase inhibitors	40	3	Recruiting
Ibrutinib	NCT02863718	• CLL	515	3	Completed
	NCT02315326	• Adult patients with newly diagnosed or relapsed or refractory PCNSL • Or relapsed or refractory SCNSL	109	1/2	Recruiting
	NCT04129710	• Relapsed/refractory PCNSL	120	2	Recruiting
	NCT04421560	• PCNSL • Recurrent cancer	37	1/2	Recruiting
	NCT01973387	• CLL • Small lymphocytic lymphoma	160	3	Completed
	NCT01744691	• CLL with 17p deletion • Small lymphocytic lymphoma with 17p deletion	145	2	Completed
Sorafenib	NCT04674345	• Acute leukemia • Relapse • HSCT	346	2/3	Recruiting
	NCT03622541	• FLT3-ITD mutation • AML	46	2	Completed
	NCT02474290	• AML • HSCT	202	2/3	Completed
Venetoclax	NCT05149378	• Acute T-lymphocytic leukemia	25	2	Recruiting
	NCT03955783	• Diffuse large B-cell lymphoma • AML • Non-Hodgkin's lymphoma	78	1	Recruiting
	NCT03625505	• AML	61	1	Completed
	NCT03504644	• B ALL • Lymphoblasts 5% or more of bone marrow nucleated cells • Recurrent adult ALL • Recurrent childhood ALL • Refractory ALL • T ALL	74	1/2	Recruiting
	NCT03319901	• Leukemia	82	1/2	Recruiting
Selinexor	NCT05698147	• Central nervous system lymphoma	30	1/2	Not yet recruiting
	NCT02249091	• Relapsed/refractory AML	42	2	Completed
	NCT02088541	• AML	317	2	Completed

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, CLL = chronic lymphoblastic leukemia, CML = chronic myeloid leukemia, CNS = central nervous system, HSCT = hematopoietic stem cell transplantation, PCNSL = primary central nervous system lymphoma, SCNSL = secondary central nervous system lymphoma, Ph = Philadelphia chromosome.

patients in CSF was significantly reduced 1 month after venetoclax administration.

4.6.3. XPO-1 inhibitors Selinexor, a nuclear export protein (SINE) selective inhibitor, inhibits exportin 1 (XPO-1) activity. XPO-1 is a crucial nucleoplasmic transporter protein in cells that is in charge of transporting proteins (including tumor suppressor proteins) out of the nucleus.[81] Because of its oncogenic involvement in exporting proteins and RNA crucial in cancer growth and treatment resistance, XPO-1 expression is linked with a poor prognosis.[81] By inhibiting XPO-1 activity, selinexor can induce cell cycle arrest and exert specific anti-cancer activity.[82] Selinexor can penetrate the BBB[82] and is allowed for the therapy of multiple myeloma and R/R DLBCL. Mouse models had proven the efficacy of selinexor in preclinical models of PCNSL, and a recent clinical case showed its clinical activity in CNSi patients with DLBCL.[83] In a PCNSL mouse model, Jiménez et al[82] proposed that combining selinexor with ibrutinib boosted antitumor immune responses, inhibiting tumor development and extending longevity. This study offers preliminary support for the implementation of selinexor and ibrutinib as novel treatment options for PCNSL patients.

4.7. Antibody-based drugs

Rituximab is a chimeric murine/human monoclonal anti-CD20 antibody. And it can be used for CD20$^+$ B lymphoid malignancies. A study by Ferreri et al[84] supported its use in patients with PCNSL. Over a median follow-up period

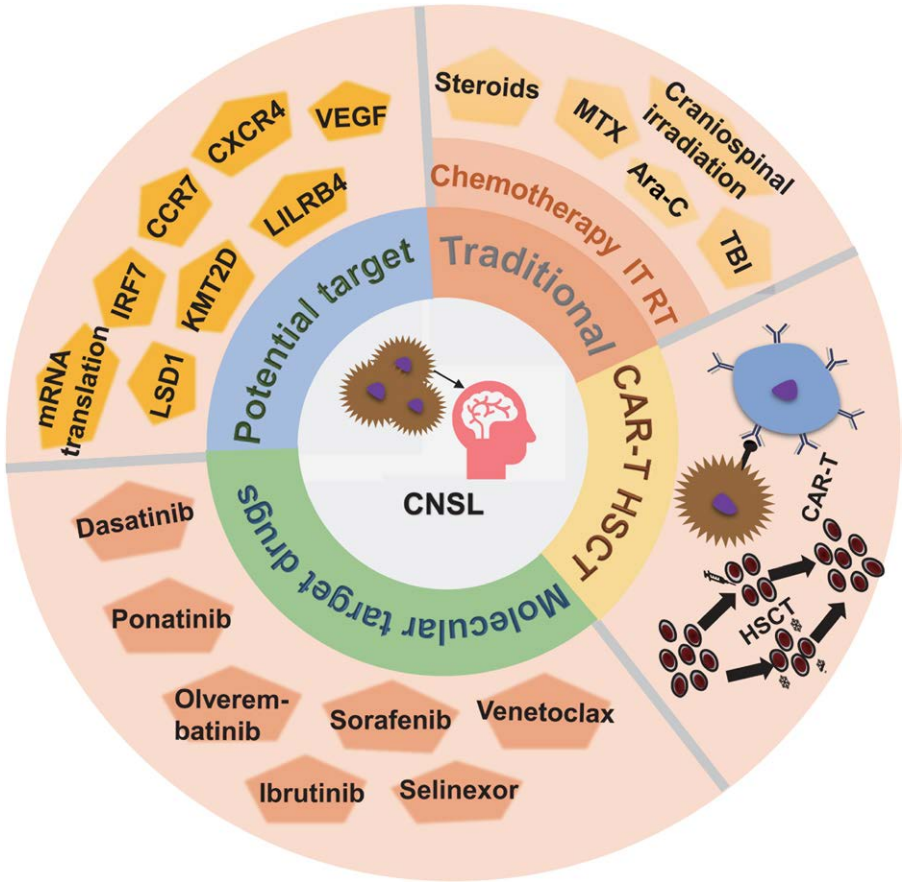

Figure 1. The current methods of central nervous system leukemia treatment. Ara-C = cytarabine, CAR-T = chimeric antigen receptor-T, CCR7 = chemokine receptor 7, CNSL = central nervous system leukemia, CXCR4 = chemokine receptor 4, HSCT = hematopoietic stem cell transplantation, IRF7 = interferon regulatory factor 7, IT = intrathecal injection, KMT2D = lysine methyltransferase 2D, LILRB4 = leukocyte immunoglobulin-like receptor B4, LSD1 = lysine-specific demethylase 1, MTX = methotrexate, RT = radiotherapy, TBI = total body irradiation, VEGF = vascular endothelial growth factor.

of 30 months, the CR rate was 49% in the group receiving rituximab and thiotepa, compared to 23% in patients using MTX and Ara-C and 30% in patients using MTX, Ara-C, and rituximab. Over a 6.5-year follow-up period, the UK NCRI trial documented 1080 DLBCL patients treated with R-CHOP, with a total CNS recurrence incidence of 1.9%.[85] This prospective trial found that including rituximab in the therapy protocol for DLBCL patients lowered the probability of CNS relapse.

However, some studies support the opposite. A randomized, open, phase 3 study indicated that including rituximab in chemotherapy could not increase EFS, OS, or progression-free survival (PFS) in PCNSL patients who were newly diagnosed.[86] Although the authors hypothesized that this outcome might be owing to the older age of the patients enrolled (median age 61 years), it remains to be verified whether rituximab is efficient in PCNSL in patients under 60. Ghose et al[87] analyzed data from 7 prospective trials and concluded that rituximab did not diminish the incidence of CNSi when compared to the CHOP regimen. Furthermore, owing to the large size of the rituximab molecule (145 kD), the CSF drug concentration following administration is only 0.1% of that in plasma.[88] The efficacy of the medicine could be impaired by such tiny concentrations.

Inotuzumab ozogamicin is a conjugate of humanized anti-CD22 monoclonal antibody with the cytotoxic antibiotic, ozogamicin. Its application in treating adult R/R ALL patients has increased CR rates and offered more patients the chance for follow-up HSCT.[89,90] Blinatumomab is a bispecific T-cell engagement (BiTE) antibody construction that binds both CD3-positive cytotoxic T cells and CD19-positive B cells, suggesting anti-leukemia efficacy in adult patients with R/R ALL.[91,92] Due to concerns about developing local inflammation, blinatumomab is not recommended for patients with existing CNSi, while it is acceptable for individuals with past CNSi.[91] In a Canadian trial comparing the efficacy of chemotherapy with new drugs like blinatumomab or inotuzumab in patients with R/R ALL when first resuscitation, CNS relapse rates were significantly lower in the new drug group than chemotherapy group (new therapy: 2.9% vs chemotherapy: 20.9%, P = .036), with OS rates and CR/CR with incomplete blood count recovery rates being similar in both groups.[93] Based on this study, novel therapies such as blinatumomab or inotuzumab may be beneficial in CNS prophylaxis. However, more large, prospective trials are necessary to demonstrate whether new therapies are beneficial in lowering CNSL recurrence.

4.8. Other findings

Chemokine receptors, like CCR7 and CXCR4, are essential for cell attachment and translocation to the CNS.[94,95] ALL cell invasion into the CNS is related to VEGF expressed and released by leukemic cells.[21] It has been demonstrated that inhibiting LILRB4 signaling by knocking down LILRB4 or employing antagonistic antibodies to LILRB4 prevented leukemic cell invasion into internal organs such as the brain.[96] Thus, targeting CCR7, CXCR4, VEGF signaling, as well as LILRB4, may be valid for the interception or cure CNSi.

Changes in the lysine-specific histone methyltransferase KMT2D gene are frequent in PCNSL patients and

connected with poor prognosis.[97] If its intrinsic relationship with PCNSL can be explored, it may help to identify potential candidates for CNSi treatment. Overexpression of lysine-specific demethylase 1 (LSD1) is an abnormality at the beginning of T-cell leukemogenesis. In a mouse xenograft model, Saito et al[98] found that the LSD1 inhibitor S2157 was efficient to prevent CNS-involved T-ALL. In the AML mouse models, Wang et al[99] reported AML cells lacking interferon regulatory factor 7 (IRF7) were characterized by high expression of vascular cell adhesion molecule 1 (VCAM1), accelerated disease progression, and accelerated CNS invasion. And these effects could be countered by blocking the VCAM1-very late antigen 4 (VLA-4) axis, representing a novel approach to managing AML CNSi. In conclusion, as we gain insight into the pathogenesis, these potential therapeutic targets have come to our attention, bringing us potential approaches for CNS disease prevention. More targeted drugs will be invented in the future, laying a solid foundation for the treatment of CNS diseases in the era of precise individualization.

5. CONCLUSION

While testicle and other extramedullary recurrences are becoming rare under current treatment regimens, CNS relapse still hampers the healing of leukemia patients. Considering the dismal prognosis once relapsing, the best strategy is to prevent CNS relapse. Past trials have proven that timely and efficient prevention protocols for high-risk patients can indeed reduce the rate of CNS relapse in patients from 75% to 4%.[4,10,11,34] Moreover, more precise adjustments should be made to the prophylaxis regimen. Receiving more frequent IT, adding rituximab to the CHOP regimen, and receiving CB pretreatment before HSCT have all demonstrated potential in trials to further lower the rate of CNSi (0%–2.9%).[42,59,85] Further experimental data are required to confirm the exact efficacy of these enhancements.

Besides traditional high-risk factors, cytogenetic, immunophenotypes, and levels of circulating biomarkers in CSF may be integrated into the rubric to improve risk stratification models and identify individuals at high risk for CNS recurrence more accurately. The combination of CC and FCM, supplemented by IC, PCR, and other diagnostic methods on the specific conditions of patients, can significantly improve the sensitivity and specificity of the diagnosis.

For patients with slight CNS infiltration, aggressive IT and systemic chemotherapy are sufficient to control CNS disease to an acceptable status. However, for some R/R patients, radiotherapy, molecular targeted drugs, and antibody-based drugs, as well as HSCT and CAR-T cellular therapy should be reasonably selected for more individualized treatment (**Fig. 1**). Targeted therapies such as CCR7 and CXCR4, and VEGF, which are related to disease pathogenesis, have also come to our attention. In addition to ensuring efficacy, we should also emphasize minimizing early and late harmful side effects for improving the quality of patient survival. And, with a further understanding of CNS disease and improved medical technology, future treatment options may change from a "one-size-fits-all" approach to a more individualized treatment according to the cytogenetic and molecular properties of patients. The prognosis for CNSL is expected to keep improving.

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