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Research Article

Primary and secondary central nervous system mature T- and NK-cell lymphomas

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ABSTRACT

Primary central nervous system (CNS) mature T- and NK-cell lymphomas are rare, only comprising 2% to 3% of all primary CNS lymphomas. Among them, peripheral T-cell lymphoma, not otherwise specified, anaplastic large cell lymphoma (ALCL), and extranodal NK/T-cell lymphoma (ENKTL) are the commonly reported histological subtypes. Secondary CNS T-cell lymphoma generally affects about 5% of patients with T- or NK-cell lymphoma, with some exceptions. Acute and lymphomatous subtypes of adult T-cell leukemia/lymphoma (ATLL) have high risk of CNS progression, may affect up to 20% of patients; ALK-positive ALCL with extranodal involvement >1 also has high risk of CNS progression. However, the impact and the optimal methodology of CNS prophylaxis remain unclear in systemic T-cell lymphomas. There are little data on the treatment strategy of primary and secondary CNS T-cell lymphoma. Treatment strategy derived from B-cell CNS primary lymphoma is generally used; this includes induction therapy with high-dose methotrexate-based regimens, followed by high-dose chemotherapy with autologous stem cell transplant in fit patients. There are unmet needs for patients who are not fit for intensive chemotherapy. The prognosis after CNS progression in T-cell lymphoma is dismal with the median overall survival of less than 1 year. New agents targeting T-cell lymphomas are emerging and should be tested in patients with mature T- and NK-cell lymphoma who suffer from CNS involvement.

Introduction

Primary and secondary involvement of the central nervous system (CNS) by mature T and NK-cell lymphomas are rare conditions and often difficult to treat. This review aims to summarize the epidemiology, histopathology, potential risk factors, and treatment options of these conditions.

Primary CNS mature T- and NK-cell lymphoma

Primary CNS lymphoma (PCNSL) comprises 1% of all non-Hodgkin's lymphoma and about 3% of all CNS malignancies [1,2]. It is a rare disease with an annual incidence of 0.3 to 0.5 per 100,000 population [3,4]. Over 90% PCNSLs are diffuse large B-cell lymphoma and the current WHO classification names the entity as primary diffuse large B-cell lymphoma of the CNS [5]. Although rare, other lymphoma subtypes can arise in CNS. T-cell primary CNS lymphomas (TPCNSL) are uncommon, and appeared much later and infrequent in literature than their B-cell counterpart. One of the first case reports of TPCNSL described a 20-year-old male with ascending paralysis. It was published in 1983 by Marsh et al and the diagnosis was made by cytology examination of the cerebrospinal fluid and brain biopsy [6]. In 1991, there were only 15 reported cases of TPCNSL [7].

TPCNSL comprises about 2% of all PCNSL in the Western countries [8-11]. Due to its rarity, the true incidence remains unknown. A Norwegian national survey identified only 3 patients had T-cell origin in all 98 patients with PCNSL (3%) between 1989 and 2003 [12]. In 2003, the International Extranodal Lymphoma Study Group (IELSG) reported 8 patients with TPCNSL in a 378 patients registry (2%) [8]. In the Surveillance, Epidemiology, and End Results (SEER) database-based study that analyzed 4375 patients with stage IE PCNSL between 1998 and 2014, 65 (1.5%) were TPCNSL [10]. A large neurosurgery referral center in Ireland reported 149 cases of PCNSL from 2007 to 2017, and only 4 (3%) of them were TPCNSL [13].

Historically, TPCNSL appeared to make up a higher percentage in all PCNSL in East Asian countries, as high as 14.3% (3 of 21) in Japan and 16.7% (7 of 42) in South Korea [14,15]. In a single-center South Korean study, TPCNSL comprised 7.4% (9 of 121) of all cases

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of PCNSL between 2000 and 2010 [16]. A Japanese national survey suggested a trend of decreasing TPCNSL/PCNSL percentage over 2 decades: 8.5% (20 of 234) between 1985 and 1994; 5.2% (6 of 115) between 1995 and 1999; and 1.7% (2 of 120) between 2000 and 2004 [9]. The reason for this decline is unclear.

Histological and clinical characteristics

Researchers did not begin to report the histological subtypes of TPCNSL until recently. In an early international study, Shenkier et al identified a total of 45 patients with TPCNSL, of which 25 had pathology reports, and 3 were subclassified as anaplastic large cell lymphoma (ALCL). Other cases were described as T-cell lymphoma (TCL) with "small," "small to medium," "pleomorphic," or "medium to large" cells, showing the challenge of calling TCL histological subtype with small biopsy sample [17]. In this study, the majority of patients were male (78%), median age was 60 years (range: 3-84), and 44% of the patient had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Involvement of a cerebral hemisphere was found in 26 patients (58%) and deeper structures in 16 patients (36%). At a median follow-up of 22 months, the median progression free survival (PFS) was 22 months and the median overall survival (OS) was 25 months. High-dose methotrexate (HD-MTX) use and better PS were associated with significantly longer disease-specific survival. Patients with a PS $\geq$2 who did not receive HD-MTX had a median survival of 3 months, compared to 43 months in those with a better PS and received HD-MTX treatment.

Menor et al summarized pathological findings of 18 patients with TPCNSL, including 15 patients with peripheral TCL-not otherwise specified (PTCL-NOS), 2 of them had $\gamma\delta$ T-cell derivation, 2 patients with ALK-negative ALCL (ALK- ALCL), and 1 with ALK-positive ALCL (ALK+ ALCL) [18]. Ten were CD8-positive, 5 were CD4-positive, and 2 were positive for Epstein-Barr virus-encoded RNA. Majority of the cases had cytotoxic phenotype, as demonstrated by positive TIA1 (87%), granzyme-B (69%), and perforin (57%). Mutation profile was available in 11 patients, and 4 (36%) patients had various somatic mutations involving *STAT3*, *STAT5B*, *JAK3*, *DNMT3A*, *KRAS*, *TET2*, and *GNB1*. There were no overlapping mutations, but 2 had mutations in the JAK/STAT pathway [19]. Most of the patients had supratentorial lesions and half had multiple lesions. Outcome data were available in 12 patients, and half of the patients died of disease at a median follow up of 5 months.

PCNSL is rare in children and adolescents. In the largest pediatric PCNSL international series, 5 of 29 patients with PCNSL (17%) had ALCL. No other T- or NK-cell lymphomas were identified. This study did not describe the ALK status of ALCL patients; however, they are likely ALK+ considering the age of patients [20].

Primary CNS extranodal NK/TCL (ENKTL) has been reported in a small Japanese case series. A total of 4 cases were diagnosed between 1984 and 2016 [21]. One of them was immunocompromised due to solid organ transplantation; this patient was treated with reduction of immunosuppressants, steroids and radiotherapy, and survived for >10 years. The other 3 patients received radiation therapy (RT) and HD-MTX; the OS was 4, 19, and 29 months, respectively. The authors also reviewed the literature and identified 10 other cases with primary CNS ENKTL. The median age of the 14 patients was 48 years (range: 21-77), male to female ratio was 1.8:1, and the median OS was 8.5 months (range: 2-29 months).

Treatment of T-cell primary CNS lymphoma

The rarity of TPCNSL prohibits meaningful clinical trials in this condition. In early case series, patients received RT, HD-MTX (>3 g/m^2), cytarabine or thiotepa in various combinations [7]. A retrospective study of TPCNSL identified that HD-MTX usage was associated with significantly longer survival, while RT was not [17]. The current treatment strategy for TPCNSL typically includes HD-MTX-based chemotherapy induction, followed by consolidation with autologous stem cell transplant (ASCT) in fit patients. This strategy is mostly derived from experiences in B-cell PCNSL, in particular primary diffuse large B-cell lymphoma of the CNS.

Whole brain RT (WBRT) was once the standard-of-care induction therapy for PCNSL, with response rates of around 80% and median OS of 10 to 20 months in different trials [22]. The major side effect of WBRT is neurotoxicity [23-26]. HD-MTX-based chemotherapy has similar efficacy to WBRT and less treatment-related neurotoxicity. Over time, HD-MTX-based chemotherapy replaced WBRT as the induction treatment of choice [25]. Commonly used regimens include MTR (methotrexate, temozolomide, rituximab), R-MVP (rituximab, MTX, vincristine, procarbazine), MBVP (MTX, BCNU, etoposide, prednisone, with or without rituximab), and MATRix (MTX, cytarabine, thiotepa, rituximab). The overall response rate (ORR) is around 70% to 97% with complete response (CR) rates of 40% to 50% with in B-cell PCNSL. MATRix, compared to HD-MTX/high-dose cytarabine with or without rituximab, had superior 2-year overall survival rate (69% vs 56% and 42%, respectively) [27]. These regimens are intensive and require highly specialized care, as life-threatening or fatal toxicities occur in 6% to 10% patients [28-32]. None of these regimens have been tested in TCL, as they involve the use of anti-CD20 antibody rituximab.

High-dose chemotherapy followed by ASCT emerged as an effective consolidation therapy in the late 1990s. Soussain et al treated 22 patients with relapse/refractory PCNSL with cytarabine-etoposide as induction, followed by TBC (thiotepa, busulfan, cyclophosphamide)-ASCT [33]. One of the patients had TPCNSL. The CR rate to induction treatment was 31%, which increased to 72% after ASCT. At the median follow up of 41.5 months, 3-year OS was 63.7%. The response and survival of the patient with TPCNSL was not discussed in this study.

Two European clinical trials addressed the question of whether ASCT is superior to WBRT as a consolidation therapy. The IELSG32 trial randomized 118 patients to receive 36Gy of WBRT or BCNU-thiotepa followed by ASCT. The 2 groups had similar 2-year PFS (80% vs 69%, hazard ratio [HR] 1.50, 95% confidence interval [CI] 0.83-2.71; $P = .17$) but neurophysiology tests suggested that WBRT was associated with cognitive impairment that was not seen in ASCT [27]. In the PRECIS study, 140 patients underwent R-MBVP induction and were randomized to TBC-ASCT or 40Gy WBRT [34]. There were no statistical differences in the 2-year or 4-year PFS or OS between each arm but the 2-year post-consolidation event-free survival rates favored ASCT (WBRT, 69%, 95% CI: 57%-83%; ASCT, 87%, 95% CI: 77%-98%; $P = .03$). Transplant-related death occurred in 5 patients (11%). The authors noted that the cognitive function of patients was better following ASCT than WBRT.

Commonly used ASCT conditioning regimens are BEAM (BCNU, etoposide, cytarabine, melphalan) and thiotepa-containing regimens, such as TBC, busulfan-thiotepa, and BCNU-thiotepa. There are no clinical trials directly comparing different conditioning regimens. In the trials using BCNU-thiotepa followed by post-ASCT WBRT, 5-year OS were around 70% and non-relapse mortality (NRM) 12% to 24% [35,36]. Three-year OS following TBC was 81% without the use of WBRT [31]. The 2- to 4-year OS following BEAM with post-ASCT WBRT were around 50% to 60% [37,38]. Researchers have looked at impact of thiotepa using transplant registry data. Kondo et al reported that thiotepa-based conditioning was associated with better PFS ($P = .019$) and lower relapse rate ($P = .042$) using data from Japan Society for Hematopoietic Cell Transplantation Registry, which included 102 patients with PCNSL treated with ASCT between 2006 and 2015 [39]. A study from the Center for International Blood and Marrow Transplant Research recently demonstrated superior 3-year PFS and a trend towards bet-

Table
Secondary TCNSL rates and outcomes reported from different centers

References	N*	N-CNS (%)† ‡	The risk of CNS progression by histological subtypes (%)§	Median overall survival after CNS involvement	Risk factors of CNS involvement&
López-Guillermo, et al.[48]	174	9 (5)	Unspecified (4) AITL (4) Angiocentric (4)	NA	NA
Mak, et al.[49]	153	12 (8)	PTCL-NOS (5) ALK+ ALCL (17) ALK- ALCL (8)	NA	NA
Ellin, et al.[50]	625	28 (4.5)	PTCL-NOS (7) ALK+ ALCL (6) ALK- ALCL (2) ALK-unknown ALCL (3)	1.1 months	Extranodal site >1 Skin involvement Gastrointestinal involvement
Gurion, et al.[51]	231	15 (6.5)	PTCL-NOS (8.2) ATLL (23.5) ENKTL (11.8) AITL (2.7) ALK- ALCL (3.6) HSTCL (11.1)	3.8 months	Extranodal site >1 IPI≥3
Chihara, et al.[52]	600	1-year cumulative incidence: 1.5% 5-year cumulative incidence: 2.1%	5-year cumulative incidence: PTCL-NOS: 1.8% AITL: 0.7% ALK+ ALCL: 5.4% ALK- ALCL: 2.1% ENKL: 3.7%	1.5 months	Extranodal site >1 ALK+ALCL
Yi, et al.[53]	228	20 (8.77)	PTCL-NOS (11.0) ALCL (15.6) AITL (5.8) EATL (12.5)	7.6 months	Elevated serum LDH Paranasal sinus involvement
Jeong, et al.[54]	301	10 (3.3)	PTCL-NOS (2.6) ALK+ALCL (7.7) ALK- ALCL (3.0) EATL (9.5)	1.4 months	NA

Abbreviations: CNS = central nervous system; AITL = angioimmunoblastic T-cell lymphoma; NA = not available; PTCL-NOS = peripheral T-cell lymphoma, not otherwise specified; ATLL = adult T-cell leukemia/lymphoma; ENKTL = extranodal NK/T-cell lymphoma; HSTCL = hepatosplenic T-cell lymphoma; IPI: international prognostic factor; LDH = lactate dehydrogenase

* Number of all patients with mature T- and NK-cell lymphoma.
† Number of patients with CNS involvement.
‡ Percentage of patients with CNS involvement.
§ Percentage of patients with CNS involvement within each histological subtype..
& By multivariate analysis

ter 3-year OS by TBC (75% and 81%) or BCNU-thiotepa (76% and 78%) over BEAM (58% and 69%) (P = .03 and 0.17 for PFS and OS, respectively). The OS of patients treated with TBC or BCNU-thiotepa were identical, but the former had higher 100-day and 1-year NRM [40].

Secondary CNS T-cell lymphoma

In mature T- and NK-cell lymphomas, CNS involvement is not as common as other extranodal sites such as the bone marrow, skin, liver, or lung [41]. One exception is adult T-cell leukemia/lymphoma (ATLL), in particular the aggressive, that is, the acute and lymphomatous subtypes. They have high frequencies (10%-20%) of CNS involvement, and CNS disease evaluation is warranted for symptomatic or high-risk patients [42-47].

The reported incidence or frequency of T-cell secondary CNSL lymphoma (SCNSL), especially in nodal TCLs such as PTCL-NOS, ALCL, angioimmunoblastic TCL (AITL), are generally less than 10% (Table). In an earlier Spanish multicenter study that analyzed 174 patients with TCL between 1986 and 1995, nine (5%) were found to have CNS involvement, including four of 95 (4%) in PTCL-NOS, one of 22 (4%) in AITL, and four of 14 (21%) in ENKTL. This study used the Revised European American Lymphoma classification and had central pathology review, however, the study didn't specify between primary and secondary CNS lymphoma [48]. Mak et al analyzed 153 patients with relapsed/refractory PTCL in British Columbia Cancer Agency Lymphoid Cancer database diagnosed between 1976 and 2010. Nine patients had SCNSL at first relapse or progression, and 3 at subsequent relapses; the rate of SCNSL at relapse was 8% [49]. The population-based registry data in Sweden included 625 patients with PTCL diagnosed between 2000 and 2009 [50]. In this cohort, 369 patients had relapsed/refractory PTCL, and 28 of them developed SCNSL. Median time from PTCL diagnosis to SCNSL was 4.3 months (range, 1.1-30 months). The incidence of SCNSL was 5.5% at 2 years, which seemed to plateau afterwards. In patients with relapsed/refractory PTCL with SCNSL, the median OS was 1.1 months compared to 3.8 months in those without (P = .082). Involvement of >1 extranodal site (HR 2.60, 95% CI: 1.07-6.29), skin (HR 3.51, 95% CI: 1.26-9.74) or gastrointestinal involvement (HR 3.06, 95% CI: 1.30-7.18) were the risk factors for SCNSL. When all 3 risk factors were present, the rate of SCNSL was 17%. Prophylactic intrathecal chemotherapy and upfront autologous stem cell transplant did not reduce the risk of SCNSL.

Several referral centers in the US have reported their experience in T-cell SCNSL. At Memorial Sloan Kettering Cancer Center, 15 patients developed SCNSL (4 at the diagnosis) among 231 patients with PTCL over the median follow up of 4.9 years. The rate of SCNSL was 6.5%. The median time to development of SCNSL was 3.4 months, and the median OS after SCNSL diagnosis was 2.6 months. Multivariate analysis showed that extranodal involvement >1 and international prognostic index 3-5 were independent risk factors for SCNSL [51].

The MD Anderson Cancer Center summarized their cohort of 600 patients with PTCL diagnosed between 1999 and 2014, including 174 PTCL-NOS, 144 AITL, 74 ALK+ ALCL, 103 ALK- ALCL, 54 ENKTL and 51 others [52]. Fifteen patients had SCNSL at the time of diagnosis and were excluded from the analysis. Thirteen

patients (4 PTCL-NOS, 1 AITL, 4 ALK+ ALCL, and 2 ENKTL) developed SCNSL with a median follow up of 57 months. Overall, 1-year and 5-year cumulative incidence of SCNSL were 1.5% (95%CI, 0.7%-2.8%) and 2.1% (95%CI, 1.1%-3.5%), respectively. In this cohort, the incidence of SCNSL was not affected by treatment, such as using hyper-CVAD/MTX. Interestingly, patients with ALK+ ALCL and had >1 extranodal involvement experienced the highest risk of SCNSL, and all occurred within 6 months of diagnosis. The one-year cumulative incidence in this patient population was 16.7% (95% CI, 4.14-36.5%).

Two centers in Korea reported their experiences in T-cell SCNSL, and the results were similar to the Western countries. At Samsung Medical Center, 20 of 228 (8.8%) patients with PTCL diagnosed between 1995 and 2009 (including 2 with CNS involvement at the time of diagnosis) had SCNSL at a median follow up of 13.9 months [53]. There seemed to be some differences in rates of CNS involvement by subtype; 15.6% in ALCL (5 of 32), 8.5 % in PTCL-NOS (11 of 119 patients), 5.8% in AITL (3 of 52 patients), and 12.5% in EATL (1 of 7 patients). In this cohort, the median time from diagnosis of TCL to SCNSL was 6.1 months (range: 0-32.1 months), and the median OS of SCNSL was 7.6 months (95% CI, 4.9-10.3 months). Elevated serum lactate dehydrogenase and paranasal sinus involvement were independent risk factors for SCNSL. The Asan Medical Center reported a rate of 3.3% (10 of 301 patients) of SCNSL in patients with PTCL diagnosed between 2003 and 2016 [54]. None had CNS disease at initial diagnosis. The median time from the diagnosis to SCNSL was 3.6 months (range, 1.1-6.2 months). SCNSL rates were 2.6% in PTCL-NOS (4 of 151 patients), 7.7% in ALK+ ALCL (3 of 39 patients), 3.0% in ALK- ALCL (1 of 33 patients), and 9.5% in EATL (2 of 21 patients). The median OS of SCNSL was only 1.4 months (range: 0.2-2.6). Subcutaneous tissue or muscle involvement and Ki-67 $\geq$ 80% were associated with higher risk of SCNSL.

SCNSL in specific PTCL subtypes has been described; however, most of the studies suffered from very small sample sizes. ENKTL is an aggressive lymphoma that primarily involves extranodal sites, especially the paranasal sinuses that are anatomical proximal to the CNS. The reported frequencies of SCNSL in ENKTL range from <6% to 13% [55-57]. Patients with SCNSL had shorter survival than those without [57,58]. An international multicenter study was conducted to develop CNS prognostic index for NK/T cell lymphoma (CNS-PINK) [59]. This study retrospectively reviewed a total of 652 patients with ENKL (399 in the training cohort, 253 in the validation cohort) who received non-anthracycline-based regimens. High CNS-PINK score was defined as ≥2 extranodal involvement and intermediate/high PINK score. The PINK score system consisted of age >60 years, Ann Arbor stage III/IV, distant lymph node involvement and non-nasal type. The 2-year risk of CNS relapse was 13.9% to 22.8% in patients with high CNS-PINK score, which was significantly higher than the 2-year risk of 4.1% to 4.5% in patients with low CNS-PINK score ($P < .001$ and $P = .038$ in the training and the validation cohort, respectively). Interestingly, patients with high score, who received SMILE-like intermediate-dose (above 2 g/m^2) methotrexate had a lower incidence of CNS relapse than those who received other regimens ($P = .029$), which is likely due to better systemic control. SMILE-like intermediate-dose methotrexate did not affect the risk of CNS relapse in patients with low CNS-PINK score.

Patients with enteropathy-associated T-cell lymphoma (EATL) may also have a high incidence of SCNSL [50·53]. Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), formerly type II EATL, is another extranodal PTCL that may have a high risk of SCNSL. In a multicenter South Korean study that included 42 patients with MEITL, none had CNS disease at diagnosis, but 4 of the 24 patients (16.7%) developed SCNSL at relapse/progression of disease [60].

Prophylaxis of CNS relapse in PTCL

CNS prophylaxis is not routinely considered in patients with PTCL besides ATLL, in which the consensus guideline from experts recommends universal CNS prophylaxis in aggressive ATLL based on prior experiences [44]· [61]. Although CNS relapse is not uncommon in high risk ENKL, EATL, MEITL, and ALK+ ALCL, administering CNS prophylaxis to high risk patients remains controversial [50,53,56,60].

The optimal method of CNS prophylaxis is also unclear. Intrathecal and/or systemic methotrexate with or without intrathecal cytarabine are commonly employed. This is derived from therapies against aggressive B-cell lymphomas and acute lymphoblastic leukemias. There is controversy among studies in aggressive B-cell lymphomas about the efficacy and modality of CNS prophylaxis, and the management of patients with high risk of CNS progression is still a major clinical challenge [62-64]. A recent retrospective study demonstrated no CNS relapse risk-reduction or survival benefit by using HD-MTX alone as CNS prophylaxis, even in patients with diffuse large B-cell lymphoma who were at high risk of CNS relapse [65]. This study, however, suggested that consolidative ASCT could more effectively reduce CNS relapse risk and prolong survival, which was likely due to better systemic control.

In aggressive ATLL, intrathecal MTX/prednisone or MTX/cytarabine/prednisone have been utilized for CNS prophylaxis, although there is uncertainty about efficacy [51]. In earlier Japanese trials, CNS relapse was seen in 1.6% of patients in JCOG9109 without routine CNS prophylaxis, and 3% to 8% of patients in JCOG9303 and JCOG9801 with routine CNS prophylaxis using the above regimens. The seemingly low rate of CNS involvement in JCOG9109, comparing to the others, might be the result of less frequent CSF examination, more disease progression and poorer survival, that patient might have already succumbed to systemic disease without having CNS manifestation [66-68]. Recently, in order to optimize CNS protection in aggressive ATLL, some centers have adopted a high-dose MTX-based induction therapy, followed by early thiotepa-based conditioning and allogeneic hematopoietic stem cell transplant [46]; this treatment strategy needs to be evaluated in prospective studies.

Treatment of T-cell Secondary CNS lymphoma

Literature is lacking regarding the treatment of T-cell SCNSL due to its heterogeneity and rarity. Patients with SCNSL face not only the same challenges as patients with PCNSL, such as poor PS and limited CNS penetration of most chemotherapy agents, but also the exposure and toxicity from prior therapy. In B-cell SCNSL, HD-MTX-based chemotherapy followed by ASCT is still the common approach, with reported 5-year OS < 50% and significant treatment-related mortality [69,70]. Reported treatment of T-cell SCNSL is heterogeneous and outcomes have been poor.

In the MD Anderson Cancer Center study, 4 of the 13 T-cell SCNSL patients received best supportive care due to poor PS, 8 received salvage chemotherapy, and 1 received local radiation [52]. None of them proceeded to ASCT, and one patient died of treatment complications after receiving an allogeneic stem cell transplant. In the Swedish registry study, all 28 patients received salvage chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CHOP-etoposide or CHOP-alemtuzumab [50]. Five patients proceeded to ASCT. The authors did not discuss the outcome of each treatment modality. In one of the South Korean studies, 3 of the 20 patients received ASCT and remained in CR for 4.6, 13.3 and 100.1 months after CNS relapse; other 3 received best supportive care, 2 received intrathecal chemotherapy only, and the remaining received various types of radiation and/or

chemotherapy [53]. As discussed before, median OS of T-cell SCNSL was less than 6 months in most of the studies [50-54].

Khawaja et al [71] retrospectively reviewed multicenter data of 84 SCNSL patients who underwent ASCT. Of note, 3 patients had T-cell SCNSL. All patients received thiotepa-based conditioning. At a median follow up of 24 months post ASCT, 2-year OS rate was 78% (95% CI, 69%-87%) and the median OS was not reached. Two patients died within 100-day of ASCT. The authors did not specifically describe the outcome of the T-cell SCNSL patients.

New agents

In the last decade, several non-chemotherapy agents, such as romidepsin, belinostat, and brentuximab-vedotin (BV) were approved for treatment of relapsed/refractory PTCL. However, these agents are not tested in patients with TPCNSL or T-cell SCNSL [72]. Patients with active CNS disease were also ineligible from participating in newer clinical trials that investigate the combination of two or more of these agents [73,74]. There are anecdotal case reports demonstrating the activity of the newer agents in patients with PTCL who have CNS disease. One case report showed durable CR by romidepsin in PTCL-NOS with CNS disease; romidepsin level was detected in the patient's CSF after administration [75]. In ALK+ ALCL, there are case reports of successful CNS disease control with alectinib, a CNS-penetrating ALK-inhibitor [76]. Although monoclonal antibodies and immunotoxins likely cross blood brain barrier, the experience of treatment of CNS disease by BV is limited and requires further data [77,78].

Immune checkpoint inhibitors have demonstrated effectiveness in metastatic CNS solid tumors [79], as well as B-cell PCNSL or SCNSL [80,81]. Both PD-1 inhibitors pembrolizumab and nivolumab, and the PD-L1 inhibitor avelumab, have shown promising activity in the treatment of relapsed/refractory ENKTL [82-84]. One case series included a patient with ENKTL who had systemic and CNS relapse. The patient had stable CNS disease after two doses of nivolumab, but unfortunately succumbed to a chest wall infection [83]. An uncommon side effect of immune checkpoint inhibitor is CNS demyelination which may mimic CNS lymphoma progression [85]. This may pose a potential challenge for future clinical trials involving immune checkpoint inhibitors in PCNSL or SCNSL.

Some agents are actively being tested in B-cell PCNSL and/or PTCL. Lenalidomide has good efficacy in B-cell PCNSL both as monotherapy and in combination [86,87]. It was also tested in patients with relapsed/refractory PTCL as monotherapy in a phase 2 clinical trial, showing an ORR of 24%, a median OS of 12 months and median PFS of 4 months [88]. An anti-CD13-TNFα fusion protein can increase the permeability of the blood-brain-barrier and deliver TNFα to the tumor vasculature. It was recently tested in 28 patients with B-cell PCNSL in combination with R-CHOP. The ORR was 75% which is higher than R-CHOP alone in historical data [89]. These new clinical data may inspire more strategies on how to effectively combat TPCNSL and T-cell SCNSL.

Conclusion

Primary and secondary CNS mature T- and NK-cell lymphomas are uncommon and heterogeneous. Certain subtypes, such as ATLL, ENKTL, EATL, MEITL, and systemic ALK+ ALCL with extranodal involvements, may have a higher risk of CNS progression, however, target patient population and optimal method of CNS prophylaxis remain unknown. The current treatment strategy for B-cell PCNSL, including HD-MTX–based induction followed by thiotepa-based conditioning and ASCT, is a viable option in the treatment of fit patients with TPCNSL or T-cell SCNSL. The advent of new therapeutic agents could expand the horizon in the future. The rarity and heterogeneity of the disease entity pose challenge for clinical investigation, and thus multi-center collaboration is essential to tackle this unmet need.

Conflicts of interest

The authors report no conflict of interest.

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