Review Article

Narrative review: secondary central nervous system lymphoma

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Abstract: Secondary central nervous system (CNS) lymphomas (SCNSL) include the systemic lymphoproliferative diseases with CNS involvement at presentation or at relapse or at both stages of disease. Potentially all lymphoproliferative diseases can present or relapse in the CNS, although with a different incidence. While for some of these the management of CNS localization can be considered standard for others a worldwide consensus on the management and treatment lacks. The incidence of CNS relapse in diffuse large B-cell lymphoma (DLBCL) is about 5%, and it is possibly slightly reduced over the last decades. Two possible reasons of this reduction are: (I) the improvement of systemic disease control obtained with the addition of rituximab to the chemotherapy; (II) the advances in identifying patients at high risk of CNS relapse and the application of prophylaxis. However, many unanswered questions remain and there is not a worldwide consensus on the criteria identifying patients at high risk of CNS and on the standard prophylaxis therapy. Patients who develop SCNSL have a poor prognosis, and the optimal treatment is unknown, and indeed often unsatisfactory. In this manuscript we report the important advances of the knowledge of this rare and fatal disease, obtained in the last years, thanks to the development of multicenter collaborations. However, this disease remains still highly fatal and the discovery of more and more efficient therapy strategies is becoming a priority. New therapeutic strategies alternative to or in combination with chemotherapy such as target and immunomodulatory therapy are being addressed in future trials. In this regard, a more accurate knowledge of the molecular and biological characteristics of this malignancy is becoming a priority for the development of innovative therapies that will be firstly investigated in refractory/relapsing patients and, if efficient, successively incorporated as part of first-line treatment.

Keywords: Secondary central nervous system lymphoma (SCNSL); central nervous system prophylaxis (CNS prophylaxis); autologous stem cell transplantation (ASCT); targeted therapy; immunomodulatory drugs (IMIDs)

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Introduction

With the term of secondary central nervous system (CNS) lymphoma (SCNSL) we indicate the systemic lymphoproliferative diseases with CNS involvement at presentation or at relapse or at both stages of disease. SCNSL may present as dissemination leptomeningeal, parenchymal, in cranial nerves or more rarely ocular. Several CNS compartments frequently are involved concomitantly or sequentially. CNS involvement in diffuse large B cell lymphoma (DLBCL) represents often a fatal event. The incidence of SCNSL at relapse in DLBCL is rare, around 5%, and possibly further reduced after the introduction of rituximab (1,2). However, the real benefit obtained with the addition of rituximab to chemotherapy is small and controversial (3-5). In the end, consensus opinion supports

that the reduction of CNS relapse in the rituximab era is a consequence of improved control of systemic disease (6,7). The pattern of CNS relapse in DLBCL after R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) appears different compared to the pattern observed in the pre-rituximab era, with relapses increasingly involving the brain parenchyma (70–80%) rather than the leptomeninges (8,9) and occurring earlier. Although a higher proportion of isolated CNS recurrences was reported in rituximab-treated patients (1,10), concurrent CNS and systemic relapses still occur in a significant proportion of cases with SCNSL (46–48%) (11). Some risk factors of CNS relapse were recognized such as high International Prognostic Index (IPI) score, involvement of more than 2 extranodal sites or involvement of specific organs defined at high risk (12-16). In these instances, CNS relapse usually occurs within the first year from diagnosis (3,11). The different scenarios, with whom the SCNSL can occur, influence the choice of therapy. However, being by definition a systemic disease, also in cases without a macroscopic systemic dissemination, the SCNSL treatment needs to be able to tackle both systemic and CNS areas of disease. The treatment usually includes two phases: induction and consolidation. The induction consists of sequential combined regimens containing agents able to cross blood brain barrier (BBB) and to penetrate within brain parenchyma and regimens containing agents that are well-known to be active in extra-CNS DLBCL. The consolidation phase can include myeloablative chemotherapy followed by autologous stem cell transplantation (HDT/ASCT), radiotherapy or standard dose chemotherapy, according to the host characteristics and to previous treatments and their responses.

This review will focus on the managements of the patients with DLBCL at high-risk of CNS relapse and on the diagnostic and therapy approaches that are increasingly widespread in clinical practice for patients with SCNSL.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/aol-20-39).

Discussion

Identification of patients with high-risk of CNS relapse lymphoma and CNS prophylaxis

Clinical risk factors of CNS relapse

SCNSL is a rare but devastating event. The identification of variables and scores with high diagnostic sensitivity to select patients at high risk for CNS relapse could permit the application of CNS prophylaxis to the only subjects with a favorable risk/benefit ratio.

In the last years, several studies tried to identify factors predicting CNS dissemination. A number of clinical characteristics (such as age more than 60 years, elevated LDH level, involvement of more than one extranodal site) were recognized to increase the risk of CNS disease. These studies' results were often discordant and their level of evidence remain low (1,3,17,18). More studies have suggested a predictive role of the IPI score (3,11,19). In the end, a large retrospective study (>2,000 patients) has analyzed the risk factors for CNS relapse. A six-factor model called 'CNS-IPI', based on the five IPI variables and kidney and/or adrenal gland involvement, was developed and validated as toll to predict the risk of CNS relapse in patients with DLBCL. CNS-IPI score permits to identify 3 risk classes: low, intermediate, and high risk, that have showed 2-year rates of CNS relapse of 0.6%, 3.4% and 10.2%, respectively. Patients belonging to low- and intermediate-risk groups, that represent around 90% of DLBCL subjects, have a risk lower than 5% and, in the absence of specific neurological symptoms, any diagnostic and therapeutic intervention may be spared. In contrast, those classified as high-risk for SCNSL have a more than 10% risk of CNS relapse and should undergo CNS-directed investigations and prophylaxis therapy (12).

Both the involvement of some extranodal sites, that are likely to be underrepresented in clinical trials but in retrospective studies have demonstrated to be associated with a high CNS relapse rates (12–16%) (11,20), and the concurrent involvement of three or more extranodal sites have demonstrated to play a crucial role in defining the risk of CNS relapse independently to CNS-IPI score (21). The inclusion of kidney and adrenal gland as the only high-risk extranodal sites in the CNS-IPI score evaluation represents one of the limitations of CNS-IPI score. Even if in large studies numbers become rather small if specific sites are analyzed separately.

More than 80% of CNS relapses seem to occur in patients with extranodal disease (22). Testis (13), breast and female reproductive organs (14,15), kidney and adrenal glands (16,23), paranasal sinus, intra-orbital (24) are among the extranodal sites that showed retrospectively to confer an increased risk of CNS dissemination (with a range incidence of CNS relapse of 10–30%). It is unclear why some of the extranodal localizations have a high risk of SCNSL, but genetic and homing factors, that are yet unknown, must play a role (13-16,23).

Molecular markers predicting CNS tropism

One possible way to improve the identification of patients with high risk of CNS relapse may be the use of biomarkers, which could layer the subjects with aggressive lymphomas on top of the clinical model.

Some biological factors have been described to be associated with an increased risk of CNS relapse in retrospective series. In particular, in high grade B cell lymphoma that harbor a MYC combined with a BCL2 and/or a BCL6 rearrangement (double-hit or triple-hit high-grade B cell lymphoma, DH/TH HGBL) and double-protein expressor lymphomas (DE), have an increased risk of CNS relapse, independent of CNS-IPI. Also, CD5 positivity has been identified as a risk factor of CNS relapse (25,26).

The increased risk in DE lymphoma was not confirmed by a subgroup analysis in patients who were enrolled in the GOYA trial and relapsed in CNS after treatment with R-CHOP or G-CHOP (obinutuzumab-CHOP). Activated B-cell-like (ABC) (HR, 5.2) or unclassified cell of origin (COO) subtypes (HR, 4.2) and high-risk CNS-IPI score were recognized as independent risk factors of CNS relapse. DE status did not demonstrate to impact on CNS relapse risk. Based on these data a consequent molecular CNS-IPI (CNS-IPI-C) was proposed (27). Three risk subgroups were identified based on the presence of high CNS-IPI score and/or ABC/unclassified COO: low risk (no risk factors), intermediate risk (1 factor), and high risk (both factors), that were associated with 2-year CNS relapse rates of 0.5%, 4.4%, and 15.2%, respectively. One of the disadvantages of the use of CNS-IPI-C model, is that the COO classification requires gene expression profiling, that is not used in general (28).

The molecular analysis, performed on the biopsy samples of the patients with CNS relapse, showed that CDKN2A loss and mutation of MYD88 were most commonly associated with CNS relapse event. In contrast, MYD88 mutations were not identified in SCNSLs in a retrospective study (29).

Lemma *et al.* have explored the role of biological markers that may confer to lymphoma cells a homing into the CNS due to a highly selective CNS tropism, in order to identify patients with a high risk of CNS recurrence. High levels of Integrin alpha 10 and PTEN on biopsy samples were associated with CNS tropism, while CD44 and cadherin-11 expressions seem to be protective of SCNSL. Due to limitations of the retrospective status and to limited samples, these results are highly preliminary and need to be validated in a larger prospective trial (30).

Prophylaxis to prevent CNS recurrence

CNS prophylaxis in DLBCL is a contentious issue. There is a wide variability in the choice of this therapeutic approach among various centers. The major reason is due to the paucity of robust, prospective studies to drive the selection of the patients who are candidate to CNS prophylaxis and the optimum method of preventing CNS relapse.

The most widely used prophylaxis is intrathecal methotrexate (MTX) (24), although its effectiveness is not established in randomized trials. A hint to at least some effect may be found in some recent studies (11,31) and the reduced incidence in testicular lymphoma (32). Other studies failed to demonstrate a benefit of intrathecal (IT) prophylaxis, probably because the pattern of CNS relapse in DLBCL is predominantly intra-parenchymal (28,33), an area that is inadequately penetrated by IT chemotherapy (34). A recent systematic review tried to solve the issue. The authors conclude that strong evidence for the use of IT prophylaxis was absent (35).

Furthermore, the optimal IT chemotherapy is not known due to the lack of randomized studies comparing the efficacy and toxicity profile of different IT regimens (MTX, Cytarabine, PEGylated Cytarabine, methylprednisolone alone or combined).

Since most of the CNS relapses nowadays present with an intra-parenchymal involvement, there has been increased focus on the use of systemic prophylaxis with intravenous high-dose methotrexate (i.v. HD-MTX). It has demonstrated its protective role in preventing CNS relapse in several studies, with a reduced CNS relapse rate to 2–5% (36-38). Since CNS disease tends to occur early, with a median of 6–8 months after DLBCL diagnosis, some authors suggested that systemic HD-MTX should be administered as early as possible after diagnosis. A recent retrospective study compared the outcome in term of CNS relapse rate and overall disease control with prophylaxis with HD-MTX intercalated to R-CHOP versus HD-MTX at the end of therapy (EOT). A higher incidence of toxicity in the intercalated HD-MTX subgroup (mucositis and febrile neutropenia), with a more frequent delay of the subsequent R-CHOP cycles (20%) was observed, although no difference in efficacy and survival were reported between two approaches. It should be mentioned here that 56% of the patients in the EOT group received also MTX it, compared to 34% of the patients that received intercalated MTX iv. It is uncertain if this has an additional role. The authors concluded that to reduce the risk of very early CNS relapse, intercalating HD-MTX with R-CHOP has

a theoretical benefit, and if this approach is used, to give the HD-MTX before day 10 to minimize toxicity and dose delays of R-CHOP. Delivery of HD-MTX at the EOT seems to be a valid alternative strategy, particularly where there is concern about fitness and ability to maintain R-CHOP dose intensity, accepting a risk that early CNS relapse may not be prevented (39).

A more intensive therapeutic approach was investigated in a recent phase 2 trial. Treatment with HD-MTX, given with the first 2 cycles of 14-day R-CHOP therapy, followed by 4 cycles of 14-day R-CHOP plus etoposide with IT cytarabine given as further CNS prophylaxis. Consolidation therapy with HD-cytarabine (HD-ARA-C) was performed in responsive patients (27). After 5 years of follow up, the failure-free survival, overall survival (OS), and CNS progression rates were 74%, 83%, and 2.3%, respectively. Treatment failure due to acute toxicity and treatment-related deaths were 6.5% and 3.6%, respectively.

No worldwide consensus exists about the optimal HD-MTX dosing and frequency. Generally, a dose of 3 g/m^2 as short (3.5–6 hours) infusion seems optimal in achieving effective CNS concentrations and avoiding serious toxicities (40).

There has been no randomized study investigating the optimal number of courses of HD-MTX as CNS prophylaxis, and a lack of worldwide consensus exists. However, two to three courses are recommended in patients without cardiac, hepatic and/or renal disfunction (41).

Lenalidomide and ibrutinib, two novel agents that were incorporated into R-CHOP therapy in two large phase 3 trials, have failed to show overall benefit for untreated patients with DLBCL (42,43). The results of a multicenter analysis to detect the potential role of lenalidomide in preventing CNS relapse was promising. Among 136 patients, who received lenalidomide in induction therapy (R2-CHOP), only one patient developed CNS relapse, after a median follow-up of 48.2 months. This promising result needs to be confirmed by larger prospective studies (44).

Whether ibrutinib and lenalidomide as well as other small molecules such as venetoclax and everolimus could specifically confer a potential protection of the CNS relapse in patients at high-risk remains an unanswered question but their ability to cross the BBB presupposes the rational for future studies.

Diagnostic and staging assessment of SCNSL

The clinical symptoms of CNS involvement may vary widely from new onset headache (50%), palsies of cranial nerves III, IV, VI, and VII, changes in neurological status (29%), seizures (23–29%) and even coma (45). CNS relapse typically presents within 8 months from diagnosis of the primary lymphoma, but late CNS relapse occurs up till 79 months (46). The CNS relapse should be confirmed by CSF and/or neuroimaging studies. In some cases, a vitrectomy or brain biopsy is required to confirm the diagnostic suspicious (47). Brain contrast-enhanced magnetic resonance imaging (MRI) and CSF examination including flow cytometry and cytology may detect CNS disease. These assessments permit to guide the choice of CNS-directed therapy and to define therapy response. MRI is the current gold standard for localizing the CNS parenchyma and leptomeningeal recurrence, having shown its superior sensitivity compared to computed tomography (CT) scan in detecting pathological lesion of CNS. Parenchymal lesions usually bright on diffusion weighted imaging, showing homogeneous enhancement. They are often multiple and localize usually in superficial cortex or periventricular sites (48). Although the imaging appearance may mimic infectious, inflammatory, or metastatic disease, a history of systemic lymphoma can orient to SCNSL diagnosis, however a confirmation by biopsy or positive CSF is advisable (49,50). Spinal MRI is recommended only if neurologic symptoms suggest spinal localization and in cases with positive CSF (48,51).

Baseline total body positron emission tomography/CT (PET/CT) should be performed in all CNS lymphoma patients to assess the extent of lymphoma involvement. In addition, PET/ CT is contemplated in the evaluation of therapy response in Non-Hodgkin Lymphomas according to Lugano criteria (52). CNS lymphomatous involvement may present as a pathological 18F-FDG uptake. Preliminary data suggest that PET/CT could represent an additional tool to the MRI in the assessment of therapy response also in CNS lymphoma, conferring metabolic information (53). However, further larger studies are needed to validate this conclusion and before its use in the clinical practice.

Ophthalmological assessment is recommended in all cases with CNS lymphoma and ocular symptoms. It includes direct ophthalmoscopy, fundus examination, fluoro-scintigraphy. In some cases, a histological or cytological confirmation could be assessed with vitrectomy and/or vitreous humor aspiration

Bone marrow biopsy and aspiration should be routinely performed at the CNS lymphoma diagnosis or relapse to detect lymphoma bone marrow involvement and/or impaired bone marrow reserve that may influence the treatment choice (*Table 1*).

Table 1 Diagnosis and staging work up in SCNSL

Test	Reason
Laboratory test	
Blood test	To assess the potential the bone marrow reserve
Full blood count; liver and renal function index; LDH; serum protein electrophoresis; serology for HIV, HCV, HBV; pregnancy test	To exclude liver and renal damage and presence of monoclonal gammopathy
	To assess prognostic factor
	To evaluate supportive anti-viral therapy
	To achieve pathogenesis information
Cerebrospinal fluid analysis	To diagnosis of CNS lymphoproliferative disease; to assess leptomeningeal dissemination
Physical-chemical exam	
Cytology	To exclude CNS infection that can be in differential diagnosis with CNS lymphoma
Immunophenotype	
CSF culture (only in cases with infection suspicious)	
Radiology and metabolic imaging	To assess CNS involvement
CNS	
Cerebral MRI; spinal MRI (only in symptomatic cases or with CSF positivity)	
Extra-CNS	To assess extra-CNS disease
^{18}FDG-PET/CT	
Testis ultrasound	
Pathology assessment	
Bone marrow biopsy and aspiration:	To assess bone marrow reserve To assess bone marrow involvement
Morphology; immunophenotype/IHC	
Biopsy of the most easily accessible extra-CNS lesion:	To diagnose SCNSL
Morphology; immunophenotype/IHC; molecular/cytogenetic analysis (myc, bcl6, bcl2)	
Stereotactic brain lesion biopsy (more rarely open brain biopsy):	To confirm CNS relapse only in these cases where the clinical and neuroimaging are not strongly suggestive
Morphology; IHC; molecular/cytogenetic analysis	
Vitrectomy and/or vitreous and/or humor aspirate (optional) (in cases with doubt ocular involvement)	To confirm ocular involvement in doubtful cases
Morphology; immunophenotype/IHC	
Ophthalmology evaluation (optional)	To exclude ocular lymphomatous infiltration
Fundoscopy and slit lamp examination, fluorescein angiography	
Cardiological assessment	To assess cardiac tolerability to chemotherapy
Echocardiography	
Electrocardiogram	

LDH, lactate dehydrogenase; HIV, human immunodeficiency viruses; HCV, hepatitis C virus; HBV, hepatitis B virus; IHC, immunohistochemistry; CNS, central nervous system; SCNSL, secondary CNS lymphoma; 18FDG-PET/CT, 18 fluorodeoxyglucose-positron emission tomography/computerized tomography; MRI, magnetic resonance imaging.

Treatment strategy

CNS involvement may be diagnosed at presentation with a systemic DLBCL, or later, as relapsed disease, either with or without systemic relapse/progression of the lymphoma. This results in three different situations of SCNSLs that may influence the choice of therapy: the patient may be treatment naïve or not, and in case of relapse it may be relevant if systemic disease is also present. However, some studies have not differentiated between upfront and relapse setting. Anyway, the systemic disease component should be incorporated in the treatment. A keystone in the treatment of CNS lymphoma is MTX. No studies have been performed that randomize between i.v and IT drug delivery. However, it is clear that a parenchymal localization is inadequately treated by intrathecal MTX only, as this penetrates only a few mm in the tumor mass.

Simultaneous CNS and systemic disease at diagnosis.
The standard treatment for systemic DLBCL is R-CHOP. To address the CNS localization, incorporation of MTX in the treatment regimen is an option. Retrospective studies show that several regimens are in use, reflecting the scarcity of well-defined prospective studies. The choice of treatment in the individual patients may have been influenced by host characteristics (comorbidity, PS, age), physician's experience and other factors.

In case of positive CSF, treatment with IT MTX may be used. Data on the outcome are scarce. In a single center retrospective study investigating the efficacy of intrathecal treatment, that included also 21 DLBCL patients, the response was 86%. The median OS was 15 months (54). To reduce the chance of systemic side-effects, such as mucositis and prolonged neutropenia, 15 mg of folinic acid orally 24 hours after the intrathecal injection is recommended.

One of the systemic treatment options is "intercalating" i.v HD-MTX between R-CHOP. As reported above, this regimen is also in use as CNS prophylaxis and it is feasible and safe (36). The HD-MTX is best given before day 9 of the R-CHOP cycle, to prevent delay of the next cycle (39). Although this regimen is in use in several centers, reports on the outcome for SCNSL are scarce and included only few patients (55). In a larger retrospective study investigating the management and outcome of 44 patients with diagnosis of SCNSL, the majority of them received R-CHOP/HD-MTX. Sixty-six percent of the patients receiving induction therapy achieved a complete remission (CR). The 3-years OS was 60%. Multivariate analysis showed that treatment with R-CHOP/HD-MTX (3.5 g/m^2) and achievement of CR were significantly associated with a better OS (56).

Another drug that penetrates the BBB effectively is HD-ARA-C. In a French retrospective study, 52 of 60 patients with SCNSL received anthracycline-based therapy. In addition, 31 of them also received HD-MTX and HD-ARA-C. Forty-one patients (68%) achieved a CR. The 3-year OS was 44% (57).

More intensive regimens than R-CHOP/HD-MTX have been used as induction regimen. In an international, multicenter, retrospective study with 80 SCNSL patients, the authors have divided the regimens used in CNS-intensive and CNS-conservative. R-Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate and cytarabine) and R-CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, high-dose cytarabine) were the most used CNS-intensive regimens. The CR rate in this subgroup was 69%. The 2-year OS was 54% (58).

It is not clear if consolidation treatment with HDT/ASCT is beneficial for this patient group. The two largest retrospective studies mentioned before, have contradictory results. Damaj *et al.* describe that almost half of the patients that were in CR after induction therapy were consolidated with ASCT. In 8 patients the conditioning regimen consisted of BEAM (carmustine (BCNU), etoposide, cytarabine and melphalan), in 8 patients a thiotepa based-regimen was used (TBC: thiotepa, busulfan, cyclophosphamide). In univariate analysis, the consolidation with ASCT was strongly associated with a better 3 year-OS (75% *vs.* 29%). No difference in outcome was found between the conditioning regimens used (57). This positive result of ASCT was not confirmed by another study, in which 19 patients received ASCT, and 14 no additional treatment (56).

CNS lymphoma in the relapse setting

The majority of CNS lymphoma dissemination is found in the relapse setting. It occurs relatively early, at a median of 8 months after initial lymphoma diagnosis. Concurrent systemic relapse is frequent. Isolated CNS relapse has a better prognosis. A retrospective database study reported the final results on 291 patients with SCNSL, of which 161 with isolated CNS relapse. Twenty-eight percent of the patients had received CNS prophylaxis, of whom 61% systemic prophylaxis. The 2-year OS was 20% (59).

The largest study into the incidence of CNS relapse

analyzed almost 2,000 patients up to 60 years old with aggressive lymphoma, who were included in several prospective studies. It revealed that 56 patients (2.6%) presented a SCNSL. The median time to development of SCNSL in this study was 7 months. Two-third of the patients developed isolated CNS disease, the others had concurrent systemic relapse or progression. The median survival after occurrence of CNS lymphoma was 5 months (3). The poor outcome of these patients is all the more disappointing considering the relatively young age of the patients in this analysis.

Even in isolated CNS relapse, the risk of systemic relapse later on is high, so treatment is usually directed against both systemic disease and the CNS compartment. Several studies have addressed this difficult situation, but they all include relatively few patients, due to the rarity of the disease. A relapse in systemic localization is generally treated with immuno-chemotherapy followed by HDT/ASCT in responsive patients. Consolidation with HDT/ASCT is valid also for CNS relapsed patients, although a conditioning regimen with CNS penetrating drugs should be used. A retrospective study from the International Primary Central Nervous System Lymphoma Study Group reported the outcome of 92 patients with SCNSL, diagnosed between 2000 and 2010. Seventy-nine percent of them received chemotherapy and 29% were consolidated with HDT/ASCT. The main reasons to refrain from ASCT were age, lack of response and poor PS/comorbidities. The median OS was 7 months. The 3-year OS was 22% for all patients, while in the group that had undergone HDT/ASCT the 3-year OS was 42% (60). The Center for International Blood and Marrow Transplant Research published the outcome of 151 patients with SCNSL comparing it with that of transplanted patients without SCNSL. They found no difference in outcome. In both groups the majority of the relapses after HDT/ASCT were outside the CNS. The 3-year OS in patients with active CNS disease at HDT/ASCT was inferior compared to those in CNS remission (31% *vs.* 58%) (61).

Prospective studies in SCNSL are rare. A German multicenter study in 30 patients used an intensive induction regimen consisting of 2 cycles of HD-MTX/ifosfamide followed by 1 cycle HD-ARA-C/thiotepa, all in combination with intrathecal therapy. This was followed by ASCT after conditioning with BCNU/thiotepa. Eighty percent of the patients had an isolated CNS relapse. A total of 24 patients (80%) received HDT/ASCT, 20 of them (67%) had achieved a response (7 CR) with induction therapy. The 2-year OS was 63% (46).

The Dutch HOVON group included 36 patients in a prospective study, treated with a regimen of R-DHAP and HD-MTX, in combination with intrathecal rituximab. Twenty patients (56%) also had a systemic relapse. Responding patients after two cycles of R-DHAP/MTX received a third cycle, and were then consolidated with ASCT after busulfan/cyclophosphamide conditioning. The overall response rate (ORR) after 2 cycles, combined CNS and systemic responses, was 53% (19/36) with CR in 22% (8/36). Fifteen patients (42%) underwent HDT/ASCT. The main reason HDT/ASCT was not performed was insufficient response. The 2-year OS was 22% (62).

A third prospective study included 38 patients with both CNS localization upfront (42%) and at relapse (58%). Treatment consisted of debulking of systemic disease with R-CHOP, if clinically indicated, induction with 2 courses of HD-MTX/HD-ARA-C/rituximab and intrathecal PEGylated-cytarabine. Patients with responsive disease proceeded with sequential HD of cyclophosphamide/ARA-C/and etoposide. Finally, patients with responsive disease received HDT/ASCT with BCNU/thiotepa–conditioning. Twenty responsive patients (19 in CR, 1 in PR) received HDT/ASCT, all achieved a CR. The 5-year OS rate of the entire population was 41%, while that of patients receiving HDT/ASCT was 68%. The majority of deaths were lymphoma-related (63). This study was the basis for a prospective study of the International Extranodal Lymphoma Study Group (IELSG): IELSG42/MARIETTA trial. The induction was intensified to 3 cycles of MATRix (HD-MTX/HD-ARA-C/thiotepa/rituximab) followed by 3 cycles of intensification R-ICE (rituximab/ifosfamide/carboplatin/etoposide), and intrathecal chemotherapy. Patients in response were consolidated with HDT/ASCT after BCNU/Thiotepa-conditioning. The results of this largest prospective study in SCNSL are recently published. Seventy-five patients with CNS involvement at presentation (43%), as isolated site of relapse (20%) or with concomitant CNS-systemic relapse (37%) received treatment. Thirty-seven patients received HDT/ASCT. The 2-year PFS was estimated at 46% for all population and at 83% for transplanted patients. Most organs involved at relapse or progression were primary sites of disease. The 2-year OS was 46% for all population and 83% for transplanted patients. Major causes of death were lymphoma-related (n=35) and toxicity (n=4). Patients with CNS involvement at presentation had the best outcome, with a 2-year PFS of 71% (64).

The UK Central and Southern lymphoma group developed the R-IDARAM regimen for treatment of SCNSL, consisting of rituximab/HD-MTX/HD-ARA-C/idarubicin/dexamethasone with IT MTX. A retrospective analysis of 23 patients with SCNSL, upfront (n=10) and at relapse (n=13) found that the ORR after 1–4 cycles was 61%. Although the numbers were small, especially the response rate in newly diagnosed patients was promising (ORR 70%). The 2-year estimated PFS and OS were 39% and 52% respectively (65).

Refractory/relapsed SCNSL: treatment options beyond chemotherapy

The result of treatment in SCNSL with curative intent is unfortunately relatively poor, and many patients will progress or relapse. Efficient therapeutic approach for refractory/relapsed (r/r) SCNSL remains a challenge.

Traditionally, symptomatic parenchymal CNS relapse can be treated with whole brain radiotherapy (WBRT). In general, this is not a curative option, but confers an improvement of symptoms. Also, treatment with dexamethasone may reduce symptoms, although for a limited time.

Salvage treatment with chemotherapy is often difficult due to patients' poor general condition and because the effective drugs that penetrate the BBB have already been used (66,67).

The interest of the clinicians now moves to investigate innovative agents beyond chemotherapy in this setting of patients.

To date, the experience reported in literature in r/r SCNSL patients treated with targeted therapy are limited to few studies on small populations.

BTK inhibitor: ibrutinib

Ibrutinib, a first-class inhibitor of Bruton tyrosine kinase (BTK), has been shown to cross the BBB and to distribute into brain tissue (68). It has been explored in r/r CNS lymphoma patients alone or in combination with chemotherapy. In a dose escalation and dose expansion phase 1 trial, ibrutinib was administered continuously (with a maximum dose of 840 mg OD) until disease progression, intolerable toxicity, or death. Twenty patients were analyzed: 13 with PCNSL and 7 with SCNSL. Ibrutinib as single agent was well tolerated both at 560 mg and at 840 mg dose level with the exception of 1 case of pulmonary aspergillosis. After a median follow-up of 1.5-year, median PFS was 4.6 months. Considering the SCNSL subgroup, 5/7 patients (71%) responded, 4 achieved CR. Median PFS for SCNSLs was 7.4 months (69).

Ibrutinib was also combined with chemotherapy after having demonstrated their synergism in killing cells of DLBCL *in vitro* (70). A phase 1b trial explored the sequential combination of ibrutinib (560 or 840 mg daily) with HD-MTX (3.5 g/m^2 every 2 weeks) for 8 courses in 9 patients with r/r PCNSL and 6 with r/r SCNSL, without active extra-CNS disease. Single-agent ibrutinib daily was administered continuously after completion of induction therapy until disease progression, intolerable toxicity, or death. Considering the subgroup of SCNSL patients, ORR was 67% (2 PR, 2 CR) (71).

Immunomodulatory drugs (IMIDs)

In systemic DLBCLs, ABC or unclassified cell of origin (COO) subtypes were recognized to have a higher risk of CNS relapse (28). The genetic alterations of ABC subtype involve the activation of B-cell receptor (BCR), Toll-like receptor (TLR), and nuclear factor-kb (NF-kB) pathways. Lenalidomide (a second-generation IMID), that carries out part of its activity inhibiting nuclear factor-kb (NF-kB) (72,73) was investigated in r/r systemic DLBCL, demonstrating to be more active in ABC than GCB subtype lymphoma.

A phase 1 study investigating safety, dose limiting toxicities (DLT) and CSF dose concentration of Lenalidomide in patients with SCNSL achieved a high CSF penetration with a minimal dose of 15 mg daily, while DLT was 20 mg (administered 21/28 days). The recommended dose was 15 mg daily. Fourteen patients were enrolled (6 r/r PCNSL and 8 r/r SCNSL, including 3 patients with active systemic lymphoma). Six SCNSLs were evaluated, 4 responded (2CR and 2 PR) and 2 progressed in CNS. The maintenance therapy demonstrated of conferring a response duration 6 times longer than which obtained after CR1 with induction therapy (74).

More recently, 2 clinical trials reported a promising efficacy and good tolerability of maintenance lenalidomide both in PCNSL and in systemic DLBCL (75,76). These results can represent the basis for future studies exploring lenalidomide treatment or maintenance in SCNSL.

Checkpoint inhibitors

The use of checkpoint inhibitors in r/r SCNSL is rarely reported. A retrospective study described the experience in 6 r/r CNS lymphoma patients (3 with r/r PCNSL and

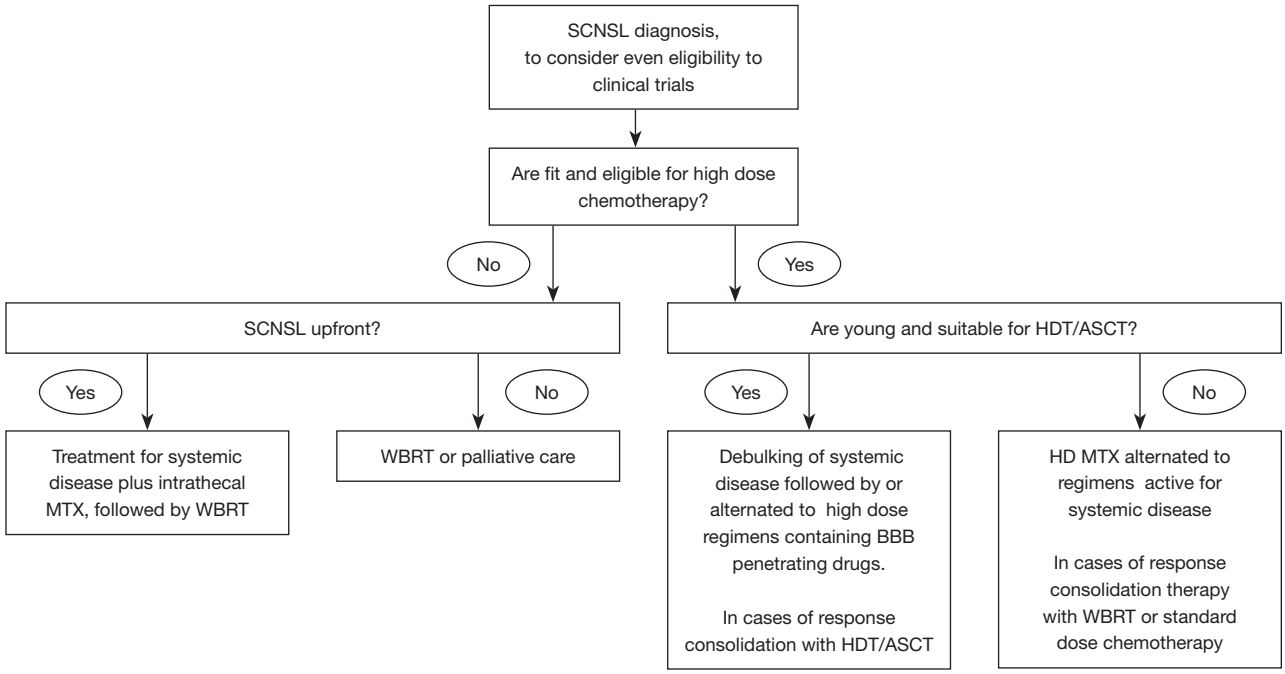

Figure 1 Flowchart on treatment options in SCNSL. SCNSL, secondary central nervous system lymphoma; WBRT, whole brain radiotherapy, HDT/ASCT, high dose therapy followed by autologous stem cell transplantation, HD MTX, high-dose methotrexate; BBB, blood brain barrier.

3 with r/r SCNSL) treated with rituximab/pembrolizumab (5 cases) or rituximab/nivolumab (1 case). An ORR of 50% with 3 CR was achieved (77). Prospective clinical trials evaluating efficacy, optimal duration, and dose of combined Checkpoint inhibitors-based regimens in r/r SCNSL are ongoing.

CAR-T cells

CAR-T cells targeting CD19 showed to be highly effective in r/r B cell lymphoproliferative diseases with ORR >80% and CR >50% (78-80). Neurological toxicity in the form of CAR-T related encephalopathy (CRE) occurred in 19% to 64% of patients treated with CAR-T cells. Due to the potential mortality by CRES, patients with CNS lymphoma were excluded from nearly all clinical trials of CAR-T cell therapy. Recent experiences in SCNSL patients treated with CAR-T-cells reported no increased incidence of CRE (81-83). These data are encouraging and hopefully may improve the dismal outcome of SCNSL.

Conclusions

SCNSL represents a strong challenge due to its rarity, the poor outcome, and the difficulty to define a standard treatment. Comparison between available studies is inherently difficult due to their heterogeneity in selection criteria of patients, that preclude a strong recommendation regarding the best therapy. Furthermore, variation in the primary treatment regimen used for systemic disease and/or for CNS prophylaxis complicates data interpretation of the results observed after the first line therapy applied for SCNSL.

The early identification of patients at high risk of CNS relapse and an efficient prophylaxis reducing the recurrence in CNS represent, to date, the more promising therapy approaches. Randomized clinical trials will be required to determine the optimal therapeutic approach for CNS prophylaxis in high-risk patients, assessing also the integration of new drugs, able to cross the BBB and to prevent CNS relapse in DLBCL.

Despite recent knowledge of the biology of CNS lymphoma and improvements in its management, SCNSL outcome is still poor. The cornerstone of treatment includes regimens with BBB penetrating drugs and regimens active for extra-CNS disease (*Figure 1*).

The role of HDT/ASCT consolidation for patients with

upfront CNS localization remains at now controversial. In the relapse setting it is generally used. A conditioning regimen with BBB penetrating drugs is important.

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