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Treatment Strategies, Outcomes, and Prognostic Factors in 291 Patients with Secondary CNS Involvement by Diffuse Large B-Cell Lymphoma

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Abstract

Purpose—Secondary CNS involvement (SCNS) is a profoundly adverse complication of diffuse large B-cell lymphoma (DLBCL). Evidence from older series indicated a median overall survival (OS) <6 months; however, data from the immuno-chemotherapy era are limited.

Methods—Patients diagnosed with SCNS during or after first-line immunochemotherapy were identified from databases and/or regional/national registries from three continents. Clinical information was retrospectively collected from medical records.

Results—In total, 291 patients with SCNS were included. SCNS occurred as part of first relapse in 254 (87%) patients and 113 (39%) had concurrent systemic relapse. With a median post-SCNS follow-up of 48 months, the median post-SCNS OS was 3.9 months and 2-year OS rate was 20% (95% CI: 15-25). In multivariable analysis of 173 patients treated with curative/intensive therapy (such as high-dose methotrexate [HDMTX] or platinum-containing regimens), age ≥ 60 years, performance status 0-1, absence of combined leptomeningeal and parenchymal involvement, and SCNS occurring after completion of first line therapy were associated with superior outcomes. Patients ≥ 60 years with performance status 0-1 and treated with HDMTX-based regimens for isolated parenchymal SCNS had a 2-year OS of 62% (95% CI: 36-80). In patients with isolated SCNS, the addition of rituximab to HDMTX-based regimens was associated with improved OS. Amongst patients with isolated SCNS in CR following intensive treatment, high-dose chemotherapy and autologous stem cell transplantation did not improve OS (P=0.9)

Conclusions—In this large international cohort of patients treated with first-line immunochemotherapy, outcomes following SCNS remain poor. However, a moderate proportion of patients with isolated SCNS who received intensive therapies achieved durable remissions.

Keywords

Diffuse large B-cell lymphoma; central nervous system; rituximab; secondary CNS; autologous stem cell transplant

Introduction

Secondary CNS involvement (SCNS) is a devastating complication of diffuse large B-cell lymphoma (DLBCL) occurring in ~5% patients.(1) High International Prognostic Index (IPI), elevated serum lactate dehydrogenase (LDH), advanced disease stage, extensive extranodal involvement, and involvement of specific extranodal sites (kidney, testes, and possibly uterus or breast) are among the most consistently reported risk factors for SCNS. (2-10) Clinical prognostic scores derived from these risk factors can identify patients at greater risk of SCNS and facilitate selection of patients who may benefit from CNS staging and prophylaxis.(6, 11) However, CNS prophylaxis does not eliminate the risk of SCNS and several patients who ultimately develop SCNS do not fulfill high-risk definitions at presentation using current risk models. (9, 11)

Patients with SCNS suffer debilitating symptoms and frequently succumb to their disease within a few months after diagnosis of SCNS.(3, 5, 6, 12) The lack of effective treatment strategies for these patients represents a major unmet clinical need. Prospective phase II and III studies have established the role of high-dose antimetabolites and consolidative therapy, including whole brain radiotherapy (WBRT) or high-dose therapy (HDT) with autologous stem cell transplantation (ASCT), in patients with primary CNS lymphoma (PCNSL). (13-17) However, similar data for patients with SCNS are limited, and only a few small phase II studies support the use of analogous treatment strategies in SCNS.(18-20) The feasibility of HDT/ASCT is limited in population-based settings due to failure of salvage treatment, toxicity, and unsuccessful stem cell harvest.(21)

Series of DLBCL patients describing the small proportion of patients who develop SCNS are typically too small to meaningfully examine prognostic factors and treatment-related differences in outcomes. To address the lack of large studies of SCNS outcome in the immuno-chemotherapy era, we evaluated an international cohort of 291 DLBCL patients who developed SCNS during or after rituximab-containing front-line therapy, and evaluated prognostic factors and treatment-related differences in the outcome of SCNS.

Patients and Methods

Study design

This retrospective cohort study included patients from clinical databases from England (Guy's and St Thomas' Hospital [London, Great Britain]), Australia (Peter MacCallum Cancer Centre [Melbourne], Monash Medical Center [Melbourne], and Sir Charles Gairdner Hospital [Perth]), Israel (Hadassah Medical Center [Jerusalem] and Rambam Health Care Campus [Haifa]), Italy (San Raffaele Scientific Institute Centre for Lymphoid Cancer [Milan]), USA (Mayo Clinic [Rochester, Minnesota] and University of Iowa [Iowa City, Iowa]) and from regional/national lymphoma registries (British Columbia Cancer Agency Centre for Lymphoid Cancer Database [Vancouver, Canada] and the Danish Lymphoma Registry [LYFO]). Anonymized data were collected locally in compliance with national and/or local regulations.

Patient identification

Patients with an initial pathologic diagnosis of DLBCL during 2001–2013 and who developed SCNS during or after frontline rituximab-containing chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone [R-CHOP] or equivalently effective regimens) were included. The surveyed period varied between centers depending on the structure of local databases/registries and availability of data. SCNS was defined as DLBCL involving the eyes (intravitreal), leptomeningeal compartment, and/or CNS parenchyma (including spinal cord) in patients without known CNS involvement at the time of first DLBCL diagnosis. Baseline CNS staging of high-risk patients was performed according to local practice but was not mandatory as part of this study. Patients with documented CNS involvement at baseline were excluded.

The diagnosis of SCNS required either pathologic (brain biopsy or cerebrospinal fluid cytology) or unequivocal radiologic (brain CT or MRI) findings together with symptoms of CNS involvement. In patients with intravitreal SCNS, symptoms combined with compatible ophthalmologic examination findings were sufficient to diagnose SCNS. In all cases, the combination of symptoms, histology, and/or imaging had to be considered adequate for the managing clinicians to initiate treatment for SCNS or palliation. As this study included patients diagnosed during a long period (2001–2013), immunohistochemistry staining for cell-of-origin and fluorescence in situ hybridization for *MYC* and *BCL2* rearrangements were not routinely done at all participating centers and were not available in the majority of patients.

Databases and medical records were reviewed for clinical characteristics and patient outcomes by local investigators. Treatment strategies were defined as curative intent intensive treatment or non-intensive and palliative/best supportive care. Curative intent treatments required intensive treatment protocols including antimetabolites such as HDMTX, high-dose cytarabine, intravitreal MTX injection (isolated intravitreal relapse) and/or platinum-based regimens with or without HDT/ASCT consolidation. HDMTX was defined as an intravenous dose of MTX intended to cross the blood brain barrier and exert a therapeutic (or prophylactic) effect throughout the different compartments of the CNS, given for any number of cycles. In the conducted analyses, one patient with isolated intravitreal SCNS treated with intravitreal MTX injections to obtain local high MTX concentration in a curative intent was included in the HDMTX group. Palliative treatment strategies included single-modality intrathecal chemotherapy, radiotherapy, and/or non-intensive systemic chemotherapy. No therapy or corticosteroids alone were coded as best supportive care. Response to frontline SCNS treatment was determined by local investigators and reported as the overall response at all involved disease sites (i.e. including systemic response in patients with concurrent disease outside CNS).

Some of the patients analyzed in this study were also included in classical studies of risk factors for SCNS, event-free survival 24 months and SCNS risk, site of SCNS according to the CNS-IPI score, transplant eligibility at the time of SCNS, as well as a case study.(11, 21-24) However, detailed analyses outcomes and prognostic factors in SCNS were not presented in these studies as there were few SCNS cases in the individual studies.

Statistical analyses

Patient characteristics were summarized using descriptive statistics. Categorical variables were compared using Fisher's exact test and continuous variables were compared using the Wilcoxon rank-sum test. Time to SCNS was defined as time from initial diagnosis of lymphoma to date of first documentation of SCNS. Overall survival (OS) was defined as the time from SCNS until death from any cause or censoring at last date of follow-up in patients still alive at the time of data collection. OS was estimated with the Kaplan-Meier method, and groups were compared using the log-rank test. Prognostic factors at the time of SCNS were analyzed for patients treated with intensive treatment protocols using uni- and multivariable Cox proportional hazards regression models. Patients with intraocular involvement were coded as having parenchymal SCNS in those analyses. All analyses were performed using Stata (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

Results

Patients

In total, 291 patients with SCNS were included (Table 1). Frontline DLBCL treatment was R-CHOP-like therapies in 96% patients. The remaining 4% received other rituximab-containing regimens such as R-ICE, R-HyperCVAD, or R-MACOP-B according to local policies. Upfront CNS prophylaxis was given to 80 (27%) patients: intrathecal chemotherapy (n=31), systemic chemotherapy (n=26), and both (n=23, included in the systemic prophylaxis group). HDMTX for systemic CNS prophylaxis was given in doses 0.4 - 4.0 g/m² (median 3 g/m²) and for a median of two cycles (range 1-6). Five patients (2%) had HIV infection. All IPI risk factors were available in 265 patients; IPI risk groups at the time of first DLBCL diagnosis were low risk (12%), low-intermediate risk (24%), high-intermediate risk (25%), and high risk (39%).(25) The CNS-IPI score was 4 in 116/265 (44%).(11)

Pathologic verification of CNS involvement was obtained in 127/291 patients (44%) with similar frequencies in patients with or without concurrent systemic involvement (P=0.5) and patients diagnosed with SCNS within two years of first pathologic diagnosis of DLBCL versus more than two years (P=0.3).

Clinicopathologic features at the time of SCNS

The median time from initial DLBCL to SCNS was 9 months (range 1-132). SCNS occurred during the course of initial DLBCL therapy in 59 (20%) patients, whereas the other 232 (80%) developed SCNS at first (n = 195), second (n = 27), or subsequent (n = 10) relapses. Patients developing SCNS during first-line therapy were younger (median age 61 years vs 65 years, P=0.015) and more likely to have concurrent systemic progression (Table 2).

Baseline CNS evaluation was performed (and was negative) in 30/59 (51%) patients who developed SCNS during initial DLBCL therapy, including CSF analysis alone (n=4), CNS imaging alone (n = 17), or both (n=9).

The most common neurological symptoms at the time of SCNS were motor deficits including ataxia, symptoms related to raised intracranial pressure (headache, vomiting, nausea), cognitive/personality changes, and visual disturbance, present in 139 (48%), 75 (26%), 68 (23%), and 53 patients (18%), respectively. At the time of SCNS, 113 (39%) patients had concomitant systemic involvement by DLBCL, which was associated with a higher rate of leptomeningeal SCNS (58% vs 39%, $P=0.001$, Table 1). Isolated parenchymal SCNS was less frequent in patients exposed to systemic CNS prophylaxis as part of initial DLBCL therapy (41% vs 57%, $P=0.041$). However, systemic prophylaxis had no significant impact on time to development of SCNS ($P=0.33$). Intrathecal CNS prophylaxis had no impact on site or time to SCNS. Because our study only included patients who developed SCNS, we are unable to evaluate the benefit of CNS prophylaxis in terms of reducing the incidence of SCNS.

Treatment of SCNS

Table 1 and Table 2 show that 118 (41%) patients received non-intensive or palliative therapy for SCNS, including best supportive care ($n=45$), systemic or intrathecal chemotherapy $\pm$ radiotherapy ($n=16$), or CNS-directed radiotherapy alone ($n=57$). Non-intensive systemic therapies included single-agent treatments with etoposide or temozolomide and multi-drug regimens containing drugs such as gemcitabine, lomustine, mitoxantrone, procarbazine, or continuation of CHOP. Radiotherapy fields included whole brain (WBRT) in 47 patients and partial brain/spinal cord in 10 patients. Treatment overview is also provided in Supplementary Figure 1.

The remaining 173 (59%) patients received curative-intent therapy with HDMTX-based ($n=151$, including six platinum-containing) or non-HDMTX-based regimens ($n=22$, including 18 platinum-containing such as ICE, GDP, or DHAP). In the former group, HDMTX was given alone ($n=72$) or as part of a multi-agent regimen ($n=79$). In the 136/151 HDMTX-treated patients with available details, the median HDMTX dose was 3.5 g/m^2 (range $1.5\text{--}8 \text{ g/m}^2$). Platinum-based regimens were used more frequently in patients with concurrent systemic involvement (19% vs 1%, $P<0.001$), while rituximab administration was similar between those with isolated vs concurrent SCNS and systemic lymphoma ($p=0.216$). Overall, 25/173 (14%) patients treated with intensive therapy proceeded to consolidative HDT and ASCT as part of first SCNS management strategy. Among those 25 patients, 19 were ≥ 64 years at the time of SCNS (Supplementary Table 1). Conditioning regimens included BEAM ($n=9$), carmustine/thiotepa ($n=6$), and TECAM ($n=6$, TECAM= thiotepa, etoposide, cytarabine, cyclophosphamide, and melphalan) and other/unknown regimens ($n=4$).

Outcome of SCNS

In total, 250 patients died (221 progressive SCNS, 18 treatment toxicity, and 11 other/unknown cause) and the median follow-up after SCNS was 48 months (range 4–140 months). The median OS for all 291 patients was 3.9 months (95% CI: 3.3–4.9) and the 2-year OS was 20% (95% CI 15–25) (Fig 1A).

The median OS for patients treated with supportive care (n=45) and non-intensive chemotherapy/radiotherapy (n=73) were 0.9 months (95% CI: 0.7-1.3) and 2.8 months (95% CI: 2.5-3.6), respectively (Fig 1B). Patients ≤ 64 years at the time of SCNS (median age) had better ECOG performance (ECOG 0-1 49% vs 31%, $P=0.003$), were more likely to be treated with intensive therapies (72% vs 47%, $P<0.001$) and had longer median OS (5.9 months vs 2.9 months, $P=0.007$) than patients >64 years at diagnosis (Supplementary Table 1).

For the 173 patients treated with intensive regimens, the median OS was only 7.5 months (95% CI: 6.0-10.3) (Fig 1B). The 25 patients who proceeded to ASCT (including 6 patients >64 years at the time of SCNS) experienced median OS 61 months, with 2-year OS 65% (95% CI: 42 - 81). Patients with documented CR after first SCNS therapy (n=67, including 20 patients undergoing HDT with ASCT) had median OS of 59.4 months (95% CI: 27.4 - 89.6, Fig 1C). Patients assessed to be in partial remission (PR, n=29) had shorter median OS of 6.2 months (95% CI: 3.9 - 16.1). The remaining patients either progressed during treatment or where not formally response assessed (palliative treatments or no treatment at all). We were unable to retrieve treatment response in one patients treated with platinum-based therapy. Patients developing SCNS during first-line DLBCL therapy had inferior median OS and 2-year survival relative to those who relapsed with SCNS after completion of first-line therapy (Table 2).

Prognostic factors at the time of SCNS

In 173 patients on intensive treatment protocols developing SCNS (Table 3 and Figure 2A-D), age >60 years, combined parenchymal and leptomeningeal SCNS (versus either compartment alone), concomitant systemic involvement, performance status >1 , and SCNS during first line therapy for DLBCL were adversely prognostic for OS in univariable analyses. In multivariable analysis, all the above factors except for concurrent systemic involvement retained a significant association with outcome.

Previous exposure to systemic HDMTX-containing CNS prophylaxis had no impact on outcome of the 173 patients treated with curative/intensive protocols (Table 3) or patients with isolated SCNS receiving HDMTX-based regimens (HR 0.91, 95%CI 0.48-1.74). The 2-year OS of younger patients (<60 years) with performance status 0-1 and treated with HDMTX-containing protocols for isolated parenchymal SCNS was 62% (95% CI: 36-80).

SCNS without concomitant systemic involvement by DLBCL

Among the 161 patients with isolated SCNS, 94 (58%) were treated with HDMTX containing treatment regimens (not including one who received both platinum and HDMTX, but including one patient with intravitreal SCNS treated with intravitreal MTX to obtain local high concentration with curative treatment intent). There was a trend toward superior OS among patients who received multi-agent regimens compared to those treated with single agent HDMTX (Fig 3A, $P=0.091$). Single modality WBRT was given to 36 patients with isolated SCNS and there was a trend toward better effect of WBRT among patients without leptomeningeal involvement compared with those patients with leptomeningeal involvement and outcomes were very poor (Fig 3B, $P=0.072$). In 38 patients with isolated SCNS and in

CR following HDMTX-based treatment, ASCT consolidation (n = 13) was not significantly associated with OS (P=0.932), although approximately half of the patients were alive at 3 years (Fig 3C). Similarly, ASCT consolidation was not associated with improved OS in the 9/17 patients with concurrent systemic disease achieving a CR following intensive induction therapy. A landmark analysis among the subset of patients alive six months after SCNS diagnosis (36/38 patients) confirmed no benefit of HDT/ASCT (P=0.793, log-rank). In the non-ASCT group, three also received consolidative WBRT and exclusion of these patients did not change the results (P=0.90). Rituximab was administered with HDMTX-based regimens to 38/94 (40%) patients with isolated SCNS and was associated with improved OS (HR 0.42, 95%CI: 0.25-0.71, P=0.001, Fig 3D). Rituximab remained associated with longer OS after adjustment for age (>60), performance status (>1), multi-agent HDMTX-based regimens vs. HDTMX alone, time of SCNS (during versus after completion of frontline DLBCL therapy), and CNS-directed radiotherapy (HR 0.39, 95%CI: 0.22 - 0.69, p = 0.001). In an analysis of all 173 patients receiving curative/intensive therapies and irrespective of systemic involvement or not (adjusted for age >60, performance status >1, SCNS during versus after completion of frontline DLBCL therapy, and CNS- directed radiotherapy), rituximab was also associated with better OS (HR 0.55, 95% CI 0.39 - 0.79, P=0.001). In a similar analysis of SCNS patients with concurrent systemic relapse treated with intensive therapies, a trend in favor of rituximab was seen (HR 0.67, 95% CI 0.38 - 1.17, P=0.16), but this analysis included only 68 patients.

Discussion

In this large, international cohort study, we investigated outcomes and prognostic factors in 291 DLBCL patients who developed SCNS during or after first-line immuno-chemotherapy. Outcomes were poor, with 2-yr OS <20% reflecting the significant proportion of patients (~40%) who received non-intensive therapies. HDMTX-based regimens were the most commonly used therapy, with 15% patients treated in this manner proceeding to consolidative ASCT. Importantly, long-term survival was seen in a small, albeit clinically relevant proportion of younger SCNS patients treated outside of clinical trials.

The median time from first pathologic diagnosis of DLBCL to SCNS was 9 months, and 20% patients developed SCNS during first-line immunochemotherapy. Patients with SCNS during induction with first-line treatment were younger, had more frequent concurrent systemic disease at progression, and experienced inferior outcomes when compared to patients with SCNS after completion of first-line treatment. Baseline CNS staging had been performed in approximately half of the patients with SCNS during first-line immunochemotherapy and we cannot exclude that at least some of the other half had occult CNS disease already at baseline. Thus, our data support CNS staging as part of the routine staging work-up in patients at high risk of SCNS based on current risk models,(4, 9, 11) as patients with concurrent CNS and systemic disease at initial diagnosis may have better outcomes with intensive treatment strategies containing both HDMTX and anthracycline-based immunochemotherapy.(26)

The ability of previous studies to address prognostic factors in SNCS has been limited by sample size, particularly in the context of heterogeneous treatment strategies.(3, 5, 6, 12,

27-30) Investigators performing prospective phase II studies of intensive protocols in the treatment of SCNS did not identify factors significantly associated with outcome, but the studies were small (all n $\leq$ 36) and included highly selected patients, limiting generalizability. (18-20, 31) Furthermore, some of these studies also included patients with known CNS involvement at the time of first DLBCL diagnosis, or patients with PCNSL.(18, 20) The present study only included patients without known CNS involvement at the time of first pathologic diagnosis of DLBCL and to limit confounding, analyses of prognostic factors were limited to patients treated with intensive regimens.

We identified a distinct subset of younger patients with isolated parenchymal SCNS without systemic involvement and with relatively favorable prognosis (2-year OS was 62% after intensive treatment). Such patients can be reassured that their outcome is unlikely to be as dismal as the typical patient with SCNS. Thus, anticipating universally poor outcomes in SCNS outside highly selective clinical trials is not supported by the literature. In fact, the 3-year OS from time of systemic relapse with DLBCL after immunochemotherapy was 40% in the CORAL study and not substantially different from that of “good-risk” SCNS arising after immunochemotherapy.(32)

We also found that the addition of rituximab to HDMTX-based regimens in the 38/94 patients with isolated SCNS was associated with a 44% reduction in the risk of death (Figure 3D). Within the limitations of small sample size and retrospective design, this finding suggests the incorporation of rituximab may be even more important than ASCT in this subgroup of patients. Interestingly, the addition of rituximab to first-line HDMTX and cytarabine for initial treatment of PCNSL was associated with a very similar risk reduction in risk of death (HR 0.63, 95% CI: 0.42-1.02, P=0.095) in the randomized IELSG-32 study. (17) Other retrospective studies of PCNSL patients receiving HDMTX-based therapy also suggest that rituximab significantly improves response rates, ability to proceed with ASCT, and outcomes when incorporated into HDMTX-based regimens.(33-35)

Data from several prospective (18-20, 31) and retrospective(21, 36-38) series demonstrate that SCNS patients who undergo ASCT have favorable PFS and OS. However, not all patients are able to undergo ASCT; in fact, retrospective series suggest that about 70% patients with SCNS who are initially eligible for ASCT eventually do not proceed, primarily due to progressive disease.(21, 36) In a phase II study of R-DHAP alternating with HDMTX and intrathecal rituximab followed by ASCT in responding patients, the overall response after initial chemotherapy was 53% (19/36) and only 42% (15/36) of the study population completed the full treatment with ASCT.(31) Although only 25 patients in our series received high dose therapy followed by ASCT, their outcomes were comparable to the published literature, with 2-year OS 65%. However, when considering only patients in CR after initial therapy, the application of ASCT was not associated with improvements in OS in the subset of patients with isolated SCNS. It is important to recognize the small number of patients in these exploratory analyses and therefore the results at best can generate hypotheses for future studies. While ASCT results from single arm-studies or observational from the literature may suffer from important biases, in particular from selection of patients with chemo sensitive disease, results generally favor ASCT if feasible. It is also possible that our results would have been more positive toward ASCT in the setting of isolated SCNS if

the myeloablative regimen thiothepa/carmustine was used more often as in primary CNS lymphoma. Ultimately, the question concerning ASCT in SCNS, especially without concurrent systemic involvement, should be addressed in randomized studies, but given the rarity and aggressiveness of isolated SCNS a prospective, randomized study will be difficult.

The study has important limitations. First, the study was retrospective with inclusion of a heterogeneous patient population treated at many different sites, probably with substantial differences in treatment policies toward SCNS. Thus, treatment effects are likely influenced to some extent by uncontrollable confounding. Second, further classification of DLBCL according to cell of origin or presence of MYC/BCL2 protein expression or gene rearrangements is not possible as these data were not performed as part of routine clinical practice in the majority of patients, which could account for the poor salvage rate in our cohort, particularly patients developing SCNS during front-line systemic therapy. Third, the observational and explorative nature of the study provide interesting hypothesis for future studies of SCNS, but we cannot make any firm recommendation for best SCNS treatment. Nevertheless, the data is still important as it can describe outcomes following various treatment approaches and prognostic factors to clinicians and patients.

Even though a small proportion of patients with SCNS experience favorable long-term outcomes with current therapies, the overall prognosis of SCNS remains poor. It is unlikely that further modifications and combinations of cytotoxic chemotherapy, rituximab, and radiation will improve outcomes over and above those reported in this and other studies. Several novel agents that cross the blood-brain barrier are being increasingly studied in primary and secondary CNS lymphomas, including ibrutinib(39, 40) and lenalidomide(41, 42). In a recent pooled analysis of two prospective studies using R-CHOP + lenalidomide (R2-CHOP) in 136 patients (18% CNS-IPI 4) with a median follow-up of 48 months, only one patient (0.7%) developed isolated CNS relapse despite minimal use of CNS prophylaxis. (43) Ongoing studies investigating the incorporation of some of these agents into upfront curative therapy for systemic DLBCL may be critical to reduce or even eliminate SCNS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- The overall prognosis of secondary CNS relapse of DLBCL remains poor.
- Few patients achieve favorable long-term outcomes with current therapies.
- Younger patients with parenchymal SCNS and no systemic involvement have a relatively good prognosis after intensive therapies.
- The addition of rituximab to HDMTX-based regimens seems to improve outcomes in the subgroup without concurrent systemic disease.

Figure 1.

A–C: Overall survival (OS) in SCNS patients according to the presence of systemic involvement at the time of SCNS (1A, 17 patients excluded due to missing information on disease status outside CNS disease) and according to treatment protocol (Intensive vs. palliative vs. best supportive care, 1B) or achieving complete remission after first-line SCNS therapy (1C, n=67 including 20 patients undergoing HDT with ASCT)

Figure 2.

A-D: Survival of patients with SCNS patients treated on intensive protocols according to age (60 years vs. >60 years, 2A), ECOG performance score (0–1 vs. 2–4, 2B), site of SCNS (parenchymal, leptomeningeal, both sites, 2C), and during/after first line treatment of SCNS, 2D)

Figure 3.

A-D: Impact of treatment selections on OS in SCNS patients without systemic involvement by DLBCL. Survival according to HDMTX treatment regimen (single agent HDMTX vs. combination therapies, 3A), single modality WBRT according to leptomeningeal involvement or not (3B), ASCT versus no ASCT in patients achieving at CR after induction treatment (3C) and outcome according to rituximab use in frontline against isolated SCNS treated with HDMTX-based regimens (3D).

Table 1

Clinicopathologic and treatment characteristics in 291 diffuse large B-cell lymphoma (DLBCL) patients at the time of secondary CNS involvement (SCNS) and according to concurrent systemic involvement or not (no information on systemic disease status in 17 patients).

	All patients (n=291)	Isolated SCNS (n=161)	SCNS with systemic involvement (n=113)	p^{β}
Median age, years (range)	64 (20–93)	64 (21–93)	63 (20–90)	0.19
Male: female ratio	1.4	1.4	1.2	0.46
Prior CNS prophylaxis, n (%)				
• No CNS prophylaxis	211 (72)	113 (70)	86 (76)	0.14
• Intrathecal prophylaxis	31 (11)	22 (14)	6 (5)	
• Systemic prophylaxis	26 (9)	13 (8)	12 (11)	
• Intrathecal and systemic prophylaxis	23 (8)	13 (8)	9 (8)	
Site of SCNS, n (%)				
• Parenchymal	152 (52)	97 (60)	42 (37)	<0.001
• Leptomeningeal	85 (29)	32 (20)	50 (44)	
• Parenchymal and leptomeningeal	47 (16)	30 (19)	16 (14)	
• Ocular	7 (3)	2 (1)	5 (5)	
ECOG performance status at the time of SCNS, n (%)				
• 0–1	117 (40)	77 (48)	37 (33)	0.013
• 2–4	174 (60)	84 (52)	76 (67)	
Time of SCNS, n (%)				
• First relapse	254 (87)	150 (93)	89 (79)	0.001
• Second relapse	27 (9)	9 (6)	16 (14)	
• Third relapse	5 (2)	2 (1)	5 (4)	
• Later relapse	5 (2)	0 (0)	3 (3)	
SCNS developing during frontline treatment, n (%)	59 (20)	24 (15)	30 (27)	0.021
Initial treatment of SCNS, n (%)				
• Non-intensive therapy				<0.001
○ Best supportive care	45 (15)	17 (11)	20 (18)	
○ Palliative chemotherapy*	16 (5)	6 (4)	10 (9)	
○ CNS-directed radiotherapy alone	57 (20)	40 (25)	15 (13)	
• Intensive therapy, n (%)				
○ HDMTX-based regimen	151 (52)	95 (59)	49 (43)	
○ Other (including platinum-based)	22 (8)	3 (2)	19 (17)	
Additional treatment for patients on intensive protocols, n (%)				

	All patients (n=291)	Isolated SCNS (n=161)	SCNS with systemic involvement (n=113)	P^{β}
• Rituximab with intensive therapy	72 (42)	39 (40)	32 (47)	0.43
• WBRT with intensive therapy	15 (9)	7 (7)	6 (9)	0.77
• ASCT consolidation with intensive therapy	25 (14)	16 (16)	9 (13)	0.66
Complete response rate, n (%)	67 (23)	49 (30)	17(15)	0.004
Median post-SCNS OS, months (95% CI)	3.9 (3.3–4.9)	6.2 (4.4–9.4)	2.9 (2.3–3.7)	<0.001 [‡]
2-year post-SCNS OS, % (95% CI)	20 (15–25)	25 (19–32)	15 (9–22)	0.041

^{β} P values reflect differences between patients with isolated SCNS and patients with concurrent systemic involvement.

* Intrathecal therapy included in the palliative chemotherapy group as well as patients treated with radiotherapy and palliative chemotherapy.

[‡]Log-rank test

Table 2

Treatment and outcome of SCNS patients diagnosed with SCNS during (n=59) or after (n=232) completion of first-line immunochemotherapy

	SCNS during frontline treatment (n=59)	SCNS after frontline treatment (n=232)	P
Median age, years (range)	61 (20–86)	65 (21–93)	0.015
Male:female ratio	1.5	1.4	0.883
Performance status	23 (39)	94 (41)	0.108
• 0–1	36 (61)	138 (59)	
• 2–4			
Site of SCNS, n (%)			0.328
• Parenchymal	28 (48)	124 (54)	
• Leptomeningeal	22 (37)	63 (27)	
• Parenchymal and leptomeningeal	7 (12)	40 (17)	
• Ocular	2 (3)	5 (2)	
Concurrent systemic involvement, n (%)			0.021
• No	24 (41)	137 (59)	
• Yes	30 (51)	83 (36)	
• Unknown	5 (8)	12 (5)	
Initial treatment of SCNS, n (%)			0.294
• Non-intensive therapy			
- Best supportive care	11 (19)	34 (15)	
- Palliative chemotherapy*	4 (7)	12 (5)	
- CNS-directed radiotherapy	6 (10)	51 (22)	
• Intensive therapy, n (%)			
- HDMTX-based regimen	33(56)	118 (51)	
- Other (including platinum-based)	5 (8)	17 (7)	
Additional treatment for patients on intensive protocols, n (%)			0.094
• Rituximab with intensive therapy	11 (29)	61 (45)	
• WBRT with intensive therapy	4 (11)	11 (8)	0.744
• ASCT consolidation with intensive therapy	3 (8)	22 (16)	0.295
Complete response rate, n (%)	12 (20%)	55 (24%)	0.729
Median post-SCNS OS, months (95% CI)	2.7 (2.0–4.0)	4.3 (3.6–5.9)	0.022 ^β
2-year post-SCNS OS, % (95% CI)	13 (6–24)	21 (16–27)	0.154

* Intrathecal therapy included in the palliative chemotherapy group.

^β Log-rank test

Table 3

Correlations between clinicopathologic features at the time of SCNS presentation and overall survival in 173 patients treated on intensive (curative) treatment protocols in first-line against SCNS. Patients with intravitreal SCNS categorized as parenchymal SCNS. HR=hazard ratio.

	N (%)	2-year OS	Crude Cox regression HR (95% CI), p	Multiple Cox regression HR (95% CI), p
Age				
• 60 years	84 (49%)	34% (24% – 44%)	1 (ref)	1 (ref)
• >60 years	89 (51%)	22% (14% – 31%)	1.44 (1.03 – 2.02), p = 0.035	1.85 (1.27 – 2.70), p = 0.001
Sex				
• Female	70 (40%)	30% (20% – 42%)	1 (ref)	1 (ref)
• Male	103 (60%)	26% (18% – 35%)	1.16 (0.82 – 1.65), p = 0.393	1.34 (0.92 – 1.94), p = 0.129
ECOG performance				
• 1	93 (54%)	34% (24% – 44%)	1 (ref)	1 (ref)
• >1 *	80 (46%)	20% (12% – 29%)	2.02 (1.44 – 2.83), p < 0.001	2.04 (1.41 – 2.94), p < 0.001
Site of SCNS				
• Parenchymal (incl. eye)	82 (47%)	36% (26% – 47%)	1 (ref)	1 (ref)
• Leptomeningeal	58 (34%)	24% (14% – 36%)	1.38 (0.94 – 2.02), p = 0.103	1.17 (0.76 – 1.79), p = 0.486
• Parenchymal and leptomeningeal	33 (19%)	13% (4% – 27%)	2.13 (1.36 – 3.33), p = 0.001	2.71 (1.68 – 4.37), p < 0.001
Systemic involvement with SCNS *				
• No	98 (57%)	32% (22% – 41%)	1 (ref)	1 (ref)
• Yes	68 (39%)	25% (15% – 36%)	1.47 (1.03 – 2.08), p = 0.032	1.47 (0.96 – 2.25), p = 0.073
SCNS during first line treatment of DLBCL				
• No	135 (78%)	38% (26% – 49%)	1 (ref)	1 (ref)
• Yes	38 (22%)	21% (14% – 30%)	1.90 (1.28 – 2.81), p = 0.001	2.16 (1.36 – 3.43), p = 0.001
Documented >1 parenchymal lesion or diffuse lesions				
• No	112 (65%)	29% (21% – 37%)	1 (ref)	1 (ref)
• Yes	61 (35%)	26% (15% – 38%)	0.99 (0.69 – 1.41), p = 0.950	0.97 (0.66 – 1.43), p = 0.891
Prior exposure to systemic CNS prophylaxis				
• No CNS prophylaxis	119 (69%)	27% (19% – 36%)	1 (ref)	1 (ref)
• Systemic +/- intrathecal CNS prophylaxis	32 (18%)	32% (13% – 53%)	0.78 (0.50 – 1.23), p = 0.287	0.84 (0.50 – 1.39), p = 0.490
• Intrathecal CNS prophylaxis	22 (13%)	56% (31% – 75%)	0.88 (0.52 – 1.48), p = 0.630	0.93 (0.53 – 1.64), p = 0.811

* 7 patients without complete systemic staging information were excluded