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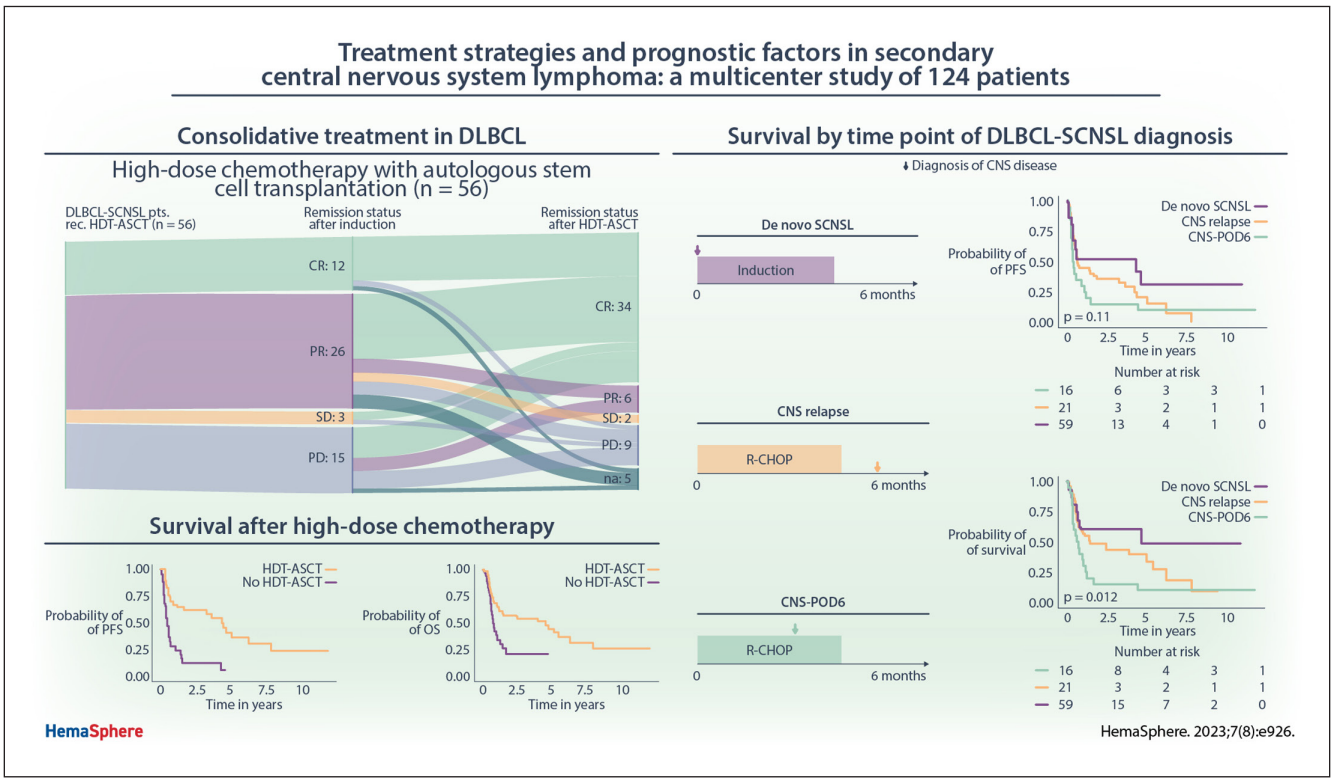
GRAPHICAL ABSTRACT



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ABSTRACT

Secondary central nervous system lymphoma (SCNSL) is a rare and difficult to treat type of Non-Hodgkin lymphoma characterized by systemic and central nervous system (CNS) disease manifestations. In this study, 124 patients with SCNSL intensively treated and with clinical long-term follow-up were included. Initial histopathology, as divided in low-grade, other aggressive, and diffuse large B-cell lymphoma (DLBCL), was of prognostic significance. Overall response to induction treatment was a prognostic factor with early responding DLBCL-SCNSL in comparison to those non-responding experiencing a significantly better progression-free survival (PFS) and overall survival (OS). However, the type of induction regime was not prognostic for survival. Following consolidating high-dose chemotherapy and autologous stem cell transplantation (HDT-ASCT), DLBCL-SCNSL patients had better median PFS and OS. The important role of HDT-ASCT was further highlighted by favorable responses and survival of patients not responding to induction therapy and by excellent results in patients with *de novo* DLBCL-SCNSL (65% long-term survival). SCNSL identified as a progression of disease within 6 months of initial systemic lymphoma presentation represented a previously not appreciated subgroup with particularly dismal outcome. This temporal stratification model of SCNSL diagnosis revealed CNS progression of disease within 6 months as a promising candidate prognosticator for future studies.

INTRODUCTION

Central nervous system (CNS) involvement in Non-Hodgkin lymphoma is a rare complication affecting <5% of patients.[1–4] It occurs mainly as relapse or progression with or without systemic manifestation after or during initial treatment of systemic lymphoma. Synchronous presentation of CNS and systemic disease at initial lymphoma diagnosis is even rarer. Both scenarios are clinically termed as secondary CNS lymphoma (SCNSL) in distinction to primary CNS lymphoma (PCNSL), a lymphoma confined to the CNS without systemic involvement at initial presentation.[5]

Clinical management of SCNSL is challenging and treatment concepts are often transferred from PCNSL due to shortage of SCNSL-specific studies. In PCNSL, thorough stepwise optimization of empirically derived chemotherapy regimens has resulted in substantial improvement of outcome.[6–8] Protocols for CNS lymphoma differ from standard immunochemotherapy such as R-CHOP, because these agents fail to cross the blood-brain barrier. Instead, high doses of drugs achieving sufficient cytotoxic levels within the CNS are combined. High-dose methotrexate (HD-MTX) remains the backbone of these protocols and is often supplemented with cytarabine (AraC), thiotepa (TT), or ifosfamide (IFO). Specifically, the combination of HD-MTX, AraC, TT, and rituximab, termed MATRix regimen, has become a widely accepted treatment for eligible PCNSL patients in Europe.[8]

In PCNSL, induction treatments such as MATRix are followed by consolidation therapy, consisting of either high-dose chemotherapy and autologous stem cell transplantation (HDT-ASCT) or whole brain radiation therapy (WBRT). Both approaches are effective and feasible in younger patients after HD-MTX-based induction and achieve promising survival rates.[9]

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To date, four prospective studies evaluating the treatment of SCNSL have been published. The German NCT01148173 phase 2 trial evaluated an induction protocol consisting of systemic HD-MTX and IFO followed by AraC and TT and subsequent consolidation with HDT-ASCT.[10] The Italian SCNSL1 trial investigated induction therapy with systemic HD-MTX, AraC, rituximab, and consolidative chemotherapies for systemic disease and HDT-ASCT for all patients.[11] In the Dutch HOVON80 trial, HD-MTX was added to R-DHAP, followed by HDT-ASCT consolidation.[12] The international prospective MARIETTA trial studied intense treatment comprising the MATRix regimen and intrathecal therapy, R-ICE, and subsequent consolidation with HDT-ASCT for responding patients.[13] In summary, all these studies lack comparator arms and therefore cannot prove the superiority of one of these approaches. This results in uncertainty when selecting the appropriate induction therapy for individual patients. Although it seems that the *de facto* standard of care in SCNSL is intensive consolidation therapy with HDT-ASCT, most patients finally do not receive HDT-ASCT.

Taken together, several questions remain to be answered regarding the optimal treatment of SCNSL. The aim of our retrospective study was to evaluate and compare efficacy and feasibility of current therapeutic concepts employed by tertiary care hematological centers in a real-world scenario. We sought to answer which induction strategies were administered for SCNSL patients, to evaluate the role of HDT-ASCT, and to assess other prognostic clinical factors. To achieve a broad dataset, retrospective data from patients with SCNSL treated in curative intention between 2008 and 2020 were collected from five participating departments.

PATIENTS AND METHODS

Inclusion criteria and data collection

Inclusion criteria were as follows: (a) patients with CNS involvement of a systemic B-cell lymphoma as determined by histopathology, cytology, and imaging; (b) adults (18 years or older); and (c) those who were intended for intensive systemic therapy with curative intention by the responsible physicians. Patients intended for HD-MTX and/or WBRT only were excluded.

The study was conducted in alignment with the Declaration of Helsinki. The institutional review boards (IRB) had approved this investigation (reg. no. 21-7212-BR, 28/3/21 UMG, B-F-2021-084, 60/21 MD).

Following IRB approval, participating centers identified and reported all consecutive patients between 2008 and 2020. There were no upper age limit nor minimal required performance status in this analysis to mirror best the real-world situation and treatment decisions. HIV-positive patients, patients with active secondary malignancy influencing management and prognosis, and non-lymphoma histopathology were excluded.

Medical data were compiled by review of patient charts by the treating physicians and were pseudonymized at each center. Data were then aggregated centrally and reviewed for plausibility and contingency. For each patient, generic biographic data (sex and age) and performance status (ECOG) at initial lymphoma diagnosis, at SCNSL diagnosis, and during subsequent the course of disease were collected and graded. Furthermore, to obtain a comparable measure of comorbidities, each patient was retrospectively evaluated using the Charlson comorbidity index (CCI) at the time of SCNSL diagnosis.[14] Details on the histological subtype were compiled from original pathology reports. Individual treatment courses including side-effects graded by Common Terminology Criteria for Adverse Events (CTCAE) for each cycle were determined.[15] Responses were reported using the Ann-Arbor and Lugano criteria.[16,17]

Clinical subgroups and end points

De novo secondary CNS lymphoma was defined as evidence of systemic and CNS involvement at diagnosis before start of the initial lymphoma therapy.[18] Progression-free survival (PFS) was defined as time from diagnosis of SCNSL until progression of disease (systemic or CNS) or until death by any cause. Progression was either defined as evidence of disease progression in imaging or by pathology/cerebrospinal fluid cytology. Overall survival (OS) was defined as the time from diagnosis of SCNSL until death from any cause.

CNS progression of disease within 6 months (CNS-POD6) was defined as first evidence of CNS involvement in a patient suffering from systemic lymphoma within 6 months of lymphoma diagnosis, that is, usually within or shortly after the initial systemic treatment in case of standard R-CHOP. In this study, the CNS-relapse category was defined as the first evidence of CNS involvement in a patient with systemic lymphoma that had been diagnosed >6 months before.

Statistical analysis

Survival times were calculated from the time of SCNSL diagnosis unless otherwise stated. Cox proportional hazards regression models were calculated for OS and PFS in patients diagnosed with SCNSL, where histopathology group, and beginning of SCNSL served as predictor variables. A combination of different clinical parameters was used to group patients, to generate Kaplan-Meier survival curves, and to perform log-rank tests.

To control for a possible lead time bias, we performed Cox regressions with time-dependent covariates HDT-ASCT and response to induction for both the univariate and multivariate analyses by using the coxph function in R with respective time intervals for covariates and events.[19] The method of Simon and Makuch was applied to estimate survival distributions with respect to time-dependent interventions.[20] Individuals at risk were initially represented in the non-HDT-ASCT (or non-responder) group. If patients received HDT-ASCT (or had a partial or complete response to induction therapy), they were censored at this time point and further followed up within the HDT-ASCT (responder) group.

The following R packages were applied: survival (version 3.4-0) and survminer (version 0.4.9). Median follow-up times were calculated using prodlim (version 2019.11.13). Swimmer plot was generated with swimplot (version 1.2.0). The Alluvial plot was generated using the online SankeyMATIC tool (https://sankeymatic.com/).

RESULTS

Study cohort

To assess the real-world clinical situation of SCNSL, we identified a total of 124 patients intensively treated between 2008 and 2020 at five tertiary hematological centers in Germany. In these patients, we observed different B-cell lymphoma subtypes, which we grouped into low-grade lymphomas, diffuse large B-cell lymphomas (DLBCL), and other aggressive lymphomas (Figure 1A).

With 96 patients, DLBCL was the most frequent histopathology in our cohort (DLBCL-SCNSL; Table 1). Other aggressive lymphomas accounted for 19 patients, and included transformed follicular lymphoma (tFL), composite lymphomas comprised of simultaneous FL and DLBCL, high-grade B-cell lymphomas (HGBL), aggressive lymphomas not otherwise specified, Richter transformation, and anaplastic large cell lymphoma (ALCL). Low-grade lymphomas made up the smallest subgroup (9 patients) and included FL, mantle cell lymphoma, and marginal zone lymphoma (Table 1).

Within the DLBCL-SCNSL cohort, 16 patients were diagnosed with synchronous systemic involvement at initial diagnosis (*de*

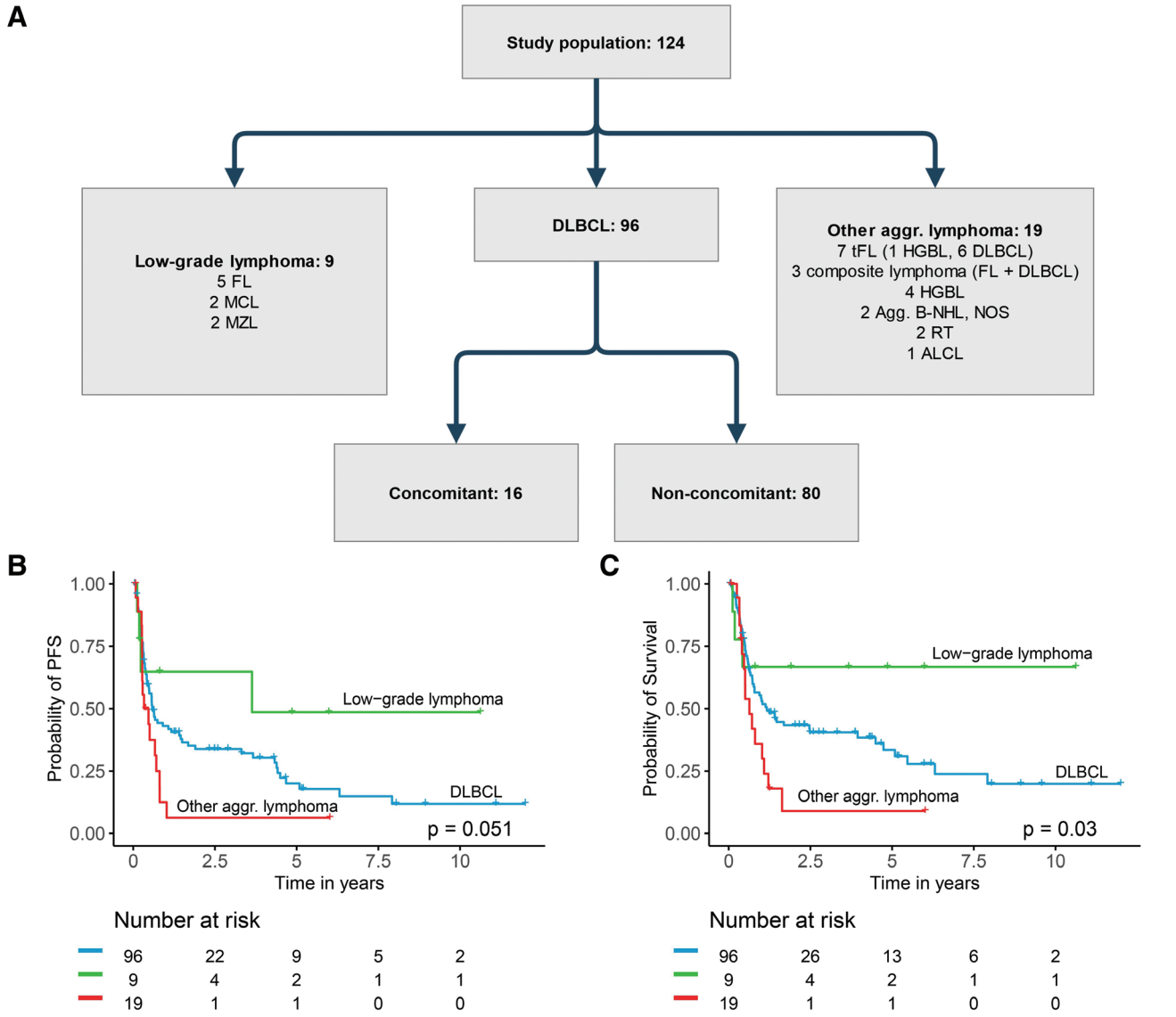

Figure 1. Cohort characteristics and survival by histopathology. (A) Consort diagram. SCNSL patients (n = 124) eligible for intensive therapy were identified at 5 hematological departments. They were stratified into 3 distinct groups by initial histopathology: low-grade lymphoma (n = 9), DLBCL (n = 96), and other aggressive lymphoma (n = 19). Low-grade lymphoma included FL, MCL, and MZL. Other aggressive lymphomas included transformed FL, composite lymphoma consisting of FL and DLBCL, HGBL, aggressive lymphomas, NOS, RT, and anaplastic large cell lymphoma. DLBCL was further divided by timing of SCNSL diagnosis in *de novo* (n = 16) and DLBCL relapse cases (n = 80). (B and C) Survival by histopathology. Stratification of SCNSL patients by initial histopathology gave subgroups with survival differences (Kaplan-Meier curves of survival; [B] progression-free survival, log-rank $P = 0.05$; [C] overall survival, log-rank $P = 0.03$). DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HGBL = high-grade B-cell lymphomas; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; NOS = not otherwise specified; RT = Richter transformation; SCNSL = secondary central nervous system lymphoma.

novo SCNSL). Most patients (n = 80) had relapsed or refractory DLBCL-SCNSL. Of those 80 patients, 55 had isolated CNS manifestations whereas 25 also showed concomitant systemic relapse. Extranodal lymphoma manifestations had been diagnosed in 58 (60%) of DLBCL-SCNSL patients at initial diagnosis. All characteristics including distributions of IPI, CNS-IPI, and lymphoma manifestations at initial diagnosis are listed in Table 1.

Histopathology of SCNSL is a prognostic factor

First, we analyzed the influence of the histopathological lymphoma subgroups on clinical outcome. Survival analysis revealed overt differences in OS (log-rank $P = 0.03$), with low-grade lymphoma being the most favorable, other aggressive lymphoma being the most unfavorable subtype, and DLBCL ranging in between these 2 subgroups. This analysis demonstrated that indeed histopathology was an important factor for outcome prediction in SCNSL (Figure 1) and prompted us to restrict subsequent analyses on DLBCL-SCNSL patients.

Role of induction treatment in DLBCL-SCNSL as prognostic factor

Next, we analyzed the response to induction therapy as a putative prognostic factor for survival in DLBCL-SCNSL. To this end, we compared responders (complete [CR] or partial remission [PR]) and non-responders (stable disease [SD] or progressive disease [PD]). Expectedly, patients with early responding DLBCL-SCNSL in comparison to those with non-responding disease experienced significantly better PFS (median PFS 3.7 months versus 39.0 months; time-dependent cox $P < 0.01$; Figure 2A) and better OS (median OS 7.2 months versus 55.8 months; time-dependent cox $P < 0.01$; Figure 2B). These results emphasized that even after excluding a potential lead time bias, response to induction treatment was an important prognostic factor in the real-world setting of DLBCL-SCNSL.

Table 1
Patient Characteristics

	All Patients (n = 124)	DLBCL Only (n = 96)
Age, median (range)	63 (27–83)	63 (27–83)
ECOG at SCNSL diagnosis		
Median (range)	1 (0–4)	1 (0–4)
0–1	67 (54.0%)	50 (52.1%)
2–3	50 (40.3%)	41 (42.7%)
4	3 (2.4%)	2 (2.1%)
NA	4 (3.2%)	3 (3.1%)
Gender		
Female	44 (35.5%)	36 (37.5%)
Male	80 (64.5%)	60 (62.5%)
Histopathology		
Diffuse large B-cell lymphoma	96 (77.4%)	96 (100%)
Follicular lymphoma	5 (4.0%)	-
Mantle cell lymphoma	2 (1.6%)	-
Marginal cell lymphoma	2 (1.6%)	-
Other aggressive lymphoma	19 (15.3%)	-
Molecular diagnostics		
MYC	11/31 (35.4%)	7/22 (31.8%)
BCL2	14/30 (46.7%)	7/21 (33.3%)
BCL6	10/27 (37.0%)	9/18 (50.0%)
Cell of origin	n = 21	n = 19
GCB	6 (28.6%)	5 (26.3%)
Non-GCB	15 (71.4%)	14 (73.7%)
Extranodal manifestations at diagnosis	n = 72	n = 58
Testicular	14 (15.9%)	11 (11.5%)
Osseous	16 (18.2%)	12 (12.5%)
Cutaneous	7 (8.0%)	6 (6.3%)
Adrenal	7 (8.0%)	6 (6.3%)
Gastrointestinal	18 (20.5%)	16 (16.7%)
Hepatic	9 (10.2%)	9 (9.4%)
Renal	8 (9.1%)	7 (7.3%)
Soft tissue	5 (5.7%)	3 (3.1%)
Other	4 (4.5%)	3 (3.1%)
>1 extranodal manifestation	12 (9.7%)	12 (12.5%)
IPI at initial lymphoma diagnosis		
Median (range)	3 (0–5)	3 (0–5)
0	6 (4.8%)	4 (4.2%)
1–2	27 (21.8%)	24 (25.0%)
3–4	44 (35.5%)	36 (37.5%)
5	6 (4.8%)	6 (6.3%)
NA	41 (33.1%)	26 (27.1%)
CNS-IPI at initial diagnosis		
Median (range)	3 (0-6)	3 (0-6)
0–1	16 (12.9%)	13 (13.5%)
2–3	43 (34.7%)	34 (35.4%)
3–4	23 (18.5%)	22 (22.9%)
NA	42 (33.9%)	27 (28.1%)
CNS-relapse type		
Isolated CNS-relapse	67/105 (63.8%)	55/80 (68.8%)
Concomitant relapse (systemic + CNS)	38/105 (36.2%)	25/80 (31.2%)
CCI score at SCNSL diagnosis		
Median (range)	4 (2–9)	5 (2–9)
2–3	37 (29.8%)	28 (29.2%)
4–5	54 (43.5%)	37 (38.5%)
6–9	32 (25.8%)	30 (31.3%)
NA	1 (0.8%)	1 (1.0%)
Induction regimen		
MITA	21 (16.9%)	12 (12.5%)
MTA	23 (18.5%)	15 (15.6%)
MA	29 (23.4%)	26 (27.1%)
MATRix	36 (29.0%)	29 (30.2%)
Other MTX-based	10 (8.1%)	9 (9.4%)
Other Non-MTX	5 (4.0%)	5 (5.2%)
Consolidation regimen		
HD-BCNU/TT	35 (28.2%)	30 (31.3%)
HD-BCNU/TT/Eto	26 (21.0%)	16 (16.7%)
HD-Busulfan/TT	10 (8.1%)	10 (10.4%)
R-DeVIC	8 (6.5%)	7 (7.3%)
WBRT	15 (12.1%)	12 (12.5%)
Other	12 (9.7%)	6 (6.3%)
None	18 (14.5%)	15 (15.6%)

Patient characteristics for all patients and for DLBCL patients.
CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HGBL = high-grade B-cell lymphomas; MA = high-dose methotrexate/cytarabine; MCL = mantle cell lymphoma; MITA = high-dose methotrexate/ifosfamide/cytarabine/thiotepa; MTA = high-dose methotrexate/cytarabine/thiotepa; MZL = marginal zone lymphoma; NOS = not otherwise specified; RT = Richter transformation; SCNSL = secondary central nervous system lymphoma; TT = thiotepa; WBRT = whole brain radiation therapy.

In our analysis, we observed local treatment preferences and classified the treatments into five induction protocols. In 26 (27%) patients HD-MTX/AraC (MA), in 29 (30%) patients the MATRix protocol, in 12 (13%) patients HD-MTX/IFO/AraC/TT (MITA), in 15 (16%) patients HD-MTX/AraC/TT (MTA), and in 14 (15%) patients other, individualized protocols had been administered, respectively. The details of all protocols are listed in Suppl. Table S1. Minor modifications comprised adjustments of treatment cycles, reduction of dosage or exclusion of HD-MTX due to impaired renal function, and addition of intrathecal therapy. One patient had died before the start of induction therapy. Five patients had only received R-TT/AraC, of whom 2 patients received subsequent HDT-ASCT, leading to durable long-term remission of >5 years in 1 patient.

Assuming better initial treatment responses to result in overall superior outcome, we next assessed survival of patients initially treated with the above detailed protocols. Median PFS in patients treated with MA, MATRix, MITA, and MTA was 6.6, 7.5, 4.4, and 52.9 months, respectively. Median OS in patients treated with these protocols was 12.1, 13.3, 12.6, and 55.8 months. However, these differences in median PFS and OS were not statistically significant, most probably due to low patient numbers in each group (log-rank $P = 0.3$ for PFS; Figure 2C; log-rank $P = 0.27$ for OS; Figure 2D). Notably, there was a positive trend for OS in MATRix treated DLBCL-SCNSL patients who finally had received HDT-ASCT (Suppl. Figure S1B). In conclusion, we did not find any type of induction treatment to be a major prognostic factor in our analysis.

Toxicity analysis

While the survival data analyses were limited to the DLBCL-SCNSL subgroup, toxicities assessed by CTCAE grading were evaluated in the full cohort considering histopathology not influencing drug side-effects. Overall, detailed toxicity data were available for 89 patients. For each patient, the highest-grade adverse event for each category occurring during any applied cycle was reported (Figure 3; Suppl. Table S2). All protocols harbored significant hematological toxicity, with most patients (89%; 79/89) exhibiting grade 4 toxicities. The only exception was observed for patients treated within the MTA protocol. Here, only 11 of 18 (61%) patients developed CTCAE grade 4 hematotoxicity. Grade 5 events were solely reported in the infectious categories for 4 patients treated with MATRix and 1 patient treated with MTA.

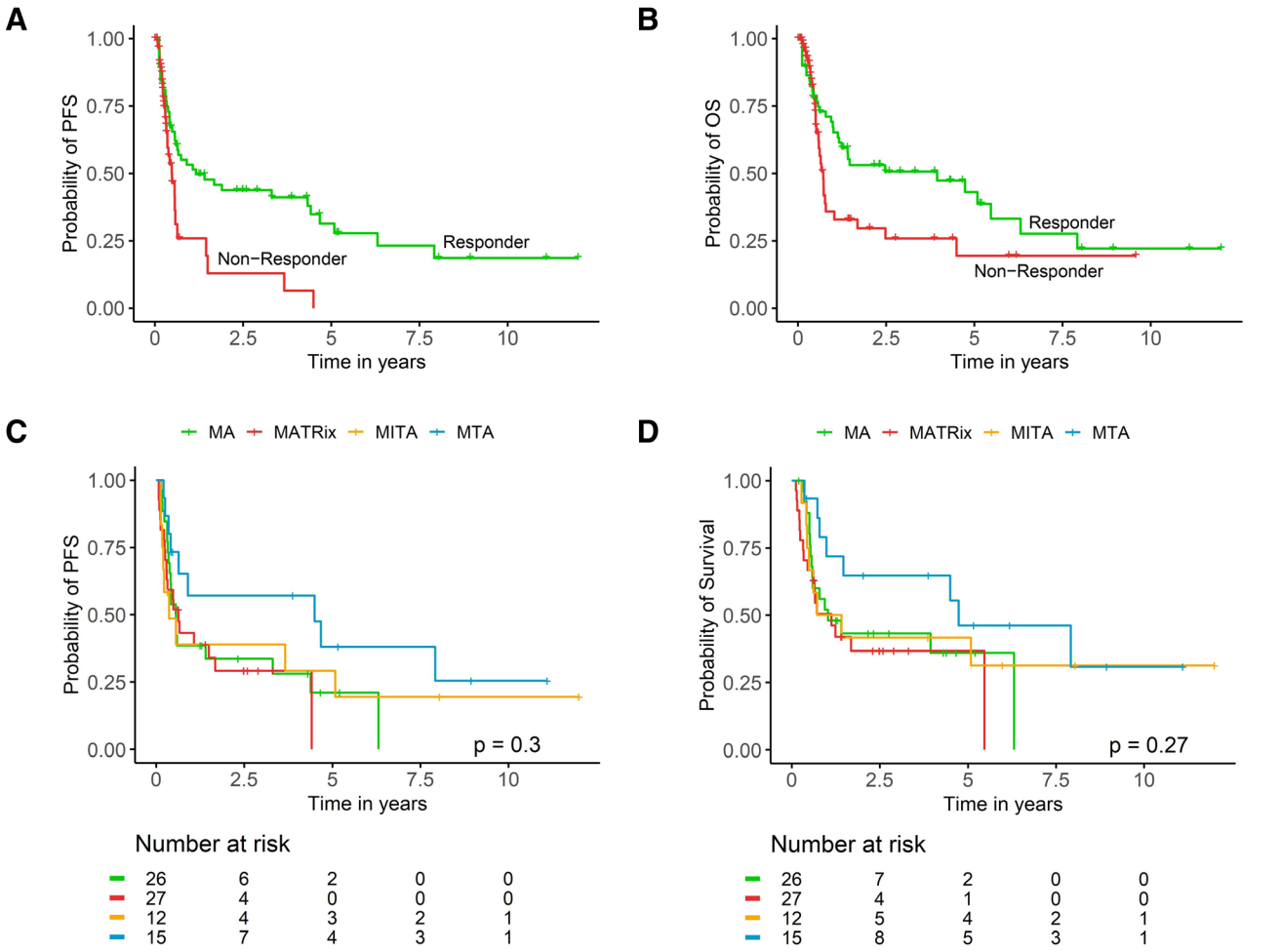

Figure 2. Role of response to induction treatment in DLBCL-SCNSL. (A and B) DLBCL-SCNSL patients responding to induction treatment (CR/PR) have a significant better survival compared with patients not responding (SD/CR; Simon-Makuch plot; [A], PFS; [B], OS). Significant differences were, however, not observed among different induction protocols (MTA, MITA, MATRix, and MA; [C], PFS, log-rank $P = 0.3$; [D], OS, log-rank $P = 0.27$). CR = complete remission; DLBCL = diffuse large B-cell lymphoma; MA = high-dose methotrexate/cytarabine; MITA = high-dose methotrexate/ifosfamide/cytarabine/thiotepa; MTA = high-dose methotrexate/cytarabine/thiotepa; OS = overall survival; PFS = progression-free survival; PR = partial remission; SCNSL = secondary central nervous system lymphoma; SD = stable disease.

Role of consolidating HDT-ASCT

In PCNSL, consolidation therapy after induction treatment is standard of care. Consolidative HDT-ASCT has mostly replaced WBRT, considering neurological long-term side-effects of CNS radiation.[9] Adopting this treatment paradigm, HDT-ASCT is an emerging standard also for SCNSL.

Accordingly, we assessed the prognostic influence of HDT-ASCT in our real-world DLBCL-SCNSL cohort (Figure 4). Of 96 patients with DLBCL-SCNSL, 56 (58%) were consolidated with HDT-ASCT, while WBRT had only been applied to 12 (12.5%) patients (Table 1). All DLBCL-SCNSL patients had been treated with a TT-based conditioning regimen, either in combination with BCNU (46/56; 82%) or busulfan (10/56; 18%; Table 1). In 16 (16.7%) patients, etoposide (450 mg/m^2 total dosage) had been added to the BCNU/TT protocol (dosage details listed in Suppl. Table S1).

Survival analysis controlling for a putative lead time bias revealed significantly better median PFS (39.0 months versus 4.6 months for patients with and without HDT-ASCT, time-dependent cox $P < 0.001$; Figure 4A) and median OS (55.8 months versus 6.9 months for patients with and without HDT-ASCT, time-dependent cox $P = 0.02$; Figure 4B) for patients who completed HDT-ASCT. Landmark analyses for HDT-ASCT stratified by pre-HDT-ASCT response and time point of SCNSL diagnosis are presented in the supplement (Suppl. Figure S4). Only 2 (3.7%) patients died during HDT-ASCT, underscoring the feasibility of this procedure in a SCNSL real-world setting.

The remission status of those 44 patients with DLBCL-SCNSL not in CR after induction improved in 31 patients (71%) following HDT-ASCT. Of note, 18 patients with progressive or stable SCNSL during induction therapy still received HDT-ASCT and 12 of these 18 DLBCL-SCNSL patients (67%) had clinically meaningful responses (CR 9 patients, PR 3 patients) after HDT-ASCT (Figure 4C). Three (17%) of these induction refractory but HDT-ASCT consolidated patients reached durable long-term survival (>5 years). The 2-year OS in this patient subgroup was 44% (Suppl. Figure S2; Suppl. Table S3).

Overall, these results demonstrated that HDT-ASCT was essential in DLBCL-SCNSL with apparent improvements in remission status and survival. HDT-ASCT administered in the challenging situation of induction refractory SCNSL could induce remissions and long-term survival in some patients.

WBRT was chosen as salvage treatment in most patients of our cohort. Landmark analysis of all 17 DLBCL-SCNSL patients undergoing WBRT is presented in the supplement. Considering application of WBRT in late disease course in most cases, PFS and OS were calculated starting from WBRT (Suppl. Figure S5).

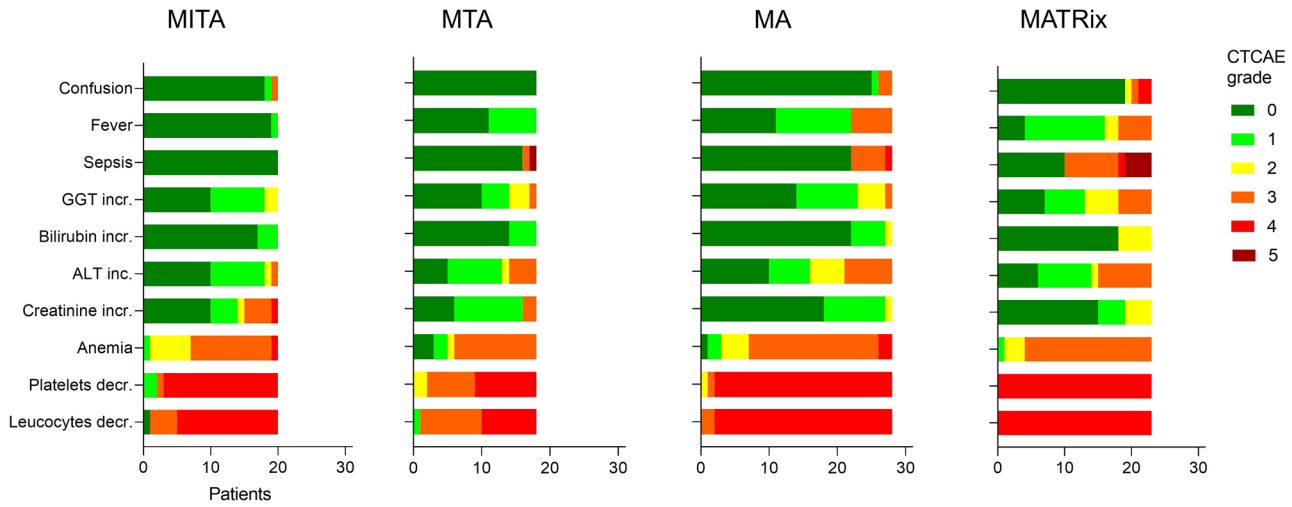

Figure 3. Toxicities of different induction protocols in SCNSL. Stacked bar graphs of relevant toxicities reported in the whole SCNSL dataset. For each category, the highest-grade toxicity (by CTCAE criteria) of all cycles applied to the patient is reported. (Numerical details listed in Suppl. Table S2). CTCAE = Common Terminology Criteria for Adverse Events; SCNSL = secondary central nervous system lymphoma.

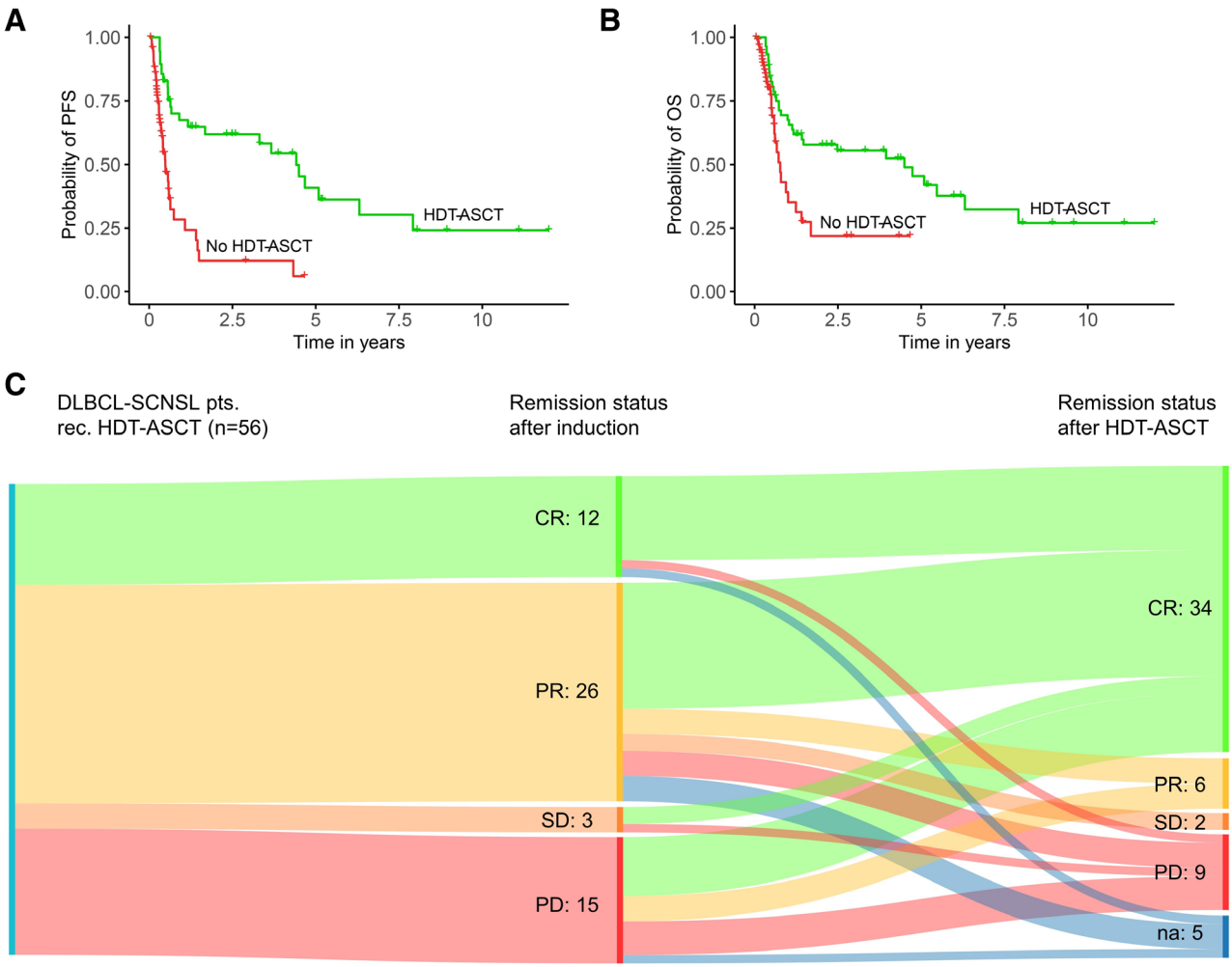

Figure 4. Role of HDT-ASCT in DLBCL-SCNSL. (A and B) Simon-Makuch plot of DLBCL-SCNSL stratified by HDT-ASCT ([A], PFS; [B], OS). (C) Alluvial plot of remission status of all DLBCL-SCNSL patients who had received HD-ASCT. DLBCL = diffuse large B-cell lymphoma; HDT-ASCT = high-dose chemotherapy and autologous stem cell transplantation; OS = overall survival; PFS = progression-free survival; SCNSL = secondary central nervous system lymphoma.

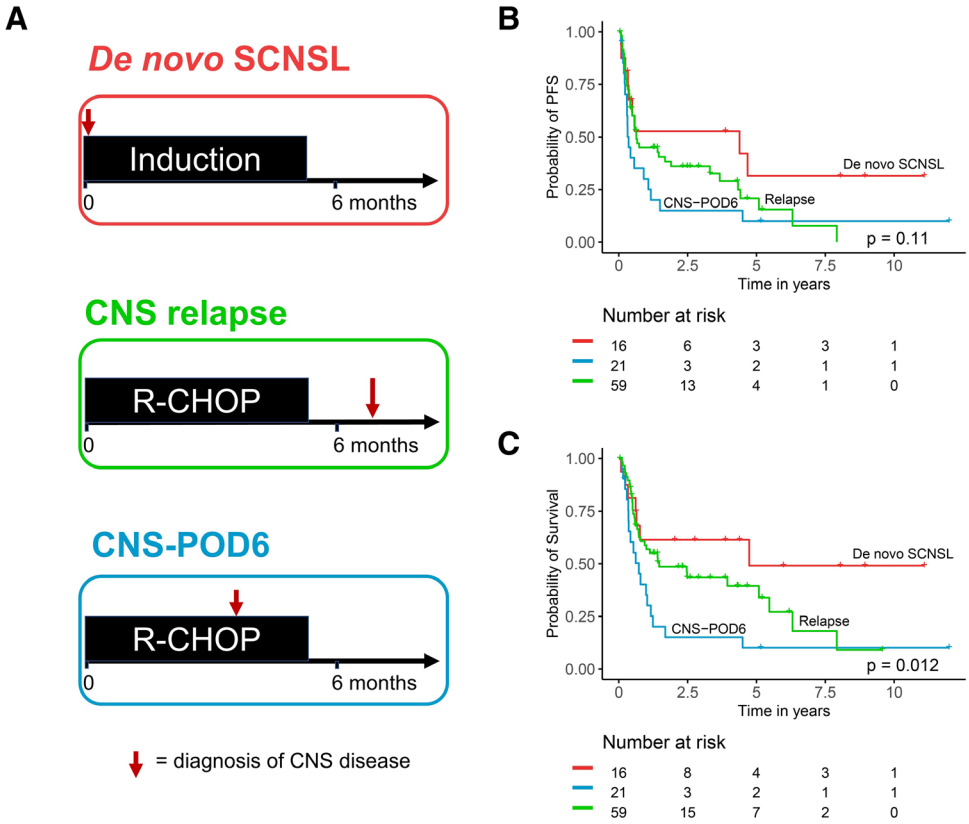

Figure 5. Temporal stratification of DLBCL-SCNSL. (A) Visualization of stratification by temporal onset in DLBCL-SCNSL. *De novo*: co-diagnosis of central and systemic lymphoma manifestation at initial diagnosis. CNS-POD6: progression of a systemic lymphoma to CNS involvement within 6 months after initial diagnosis. CNS-relapse: CNS involvement later than 6 months after systemic lymphoma diagnosis. (B and C) Kaplan-Meier curves of DLBCL-SCNSL survival stratified by time of SCNSL diagnosis ([B]: PFS, log-rank $P = 0.11$; [C]: OS, log-rank $P = 0.01$). CNS-POD6 = central nervous system progression of disease within 6 months; DLBCL = diffuse large B-cell lymphoma; OS = overall survival; PFS = progression-free survival; SCNSL = secondary central nervous system lymphoma.

Time point of SCNSL diagnosis as prognostic factor

Next, we hypothesized that the time point of SCNSL diagnosis might be of prognostic relevance. Based on our SCNSL cohort, three clinical scenarios were distinguished (Figure 5A): *de novo* SCNSL with co-occurrence of CNS and systemic lymphoma manifestation at initial diagnosis versus early manifestation of SCNSL within 6 months after initial diagnosis of systemic lymphoma (CNS-POD6) versus SCNSL occurrence after >6 months following initial lymphoma diagnosis (CNS-relapse).

Based on this clinical stratification, we separately analyzed survival of our DLBCL-SCNSL patients. Median PFS was 51.7 months in *de novo* SCNSL, 7.5 months in CNS-relapse, and 4.2 months in CNS-POD6 patients, respectively (log-rank $P = 0.11$; Figure 5B). Median OS was 55.8 months in *de novo* SCNSL, 17.3 months in CNS-relapse, and 8.6 months in CNS-POD6 patients, respectively (log-rank $P = 0.01$; Figure 5C). These data suggested distinction of SCNSL patients based on the onset of CNS disease to be a meaningful prognostic tool, which should be orthogonally validated and considered within future clinical studies.

De novo DLBCL-SCNSL

De novo systemic and CNS lymphoma at initial diagnosis is particularly rare and treatment recommendations are lacking. Therefore, we performed detailed analyses of this SCNSL subtype (Figure 6). In total, 16 (17%) of our 96 DLBCL-SCNSL patients had been diagnosed with overt de novo SCNSL. Overall, these patients in our cohort demonstrated a favorable PFS (median PFS 51.7 months; Figure 6A) and promising OS (median OS 55.8 months; Figure 6B). Most of our patients had received HDT-ASCT (11/16 patients; 69%). These intensively treated patients exhibited an excellent PFS (median 55.1 months; Figure 6C) and OS (median not reached; Figure 6D). Remarkably, the only long-time survivor who had not undergone HDT-ASCT had finally been treated with CAR-T cells. Patients not receiving HDT-ASCT had died of sepsis (n = 2) and PD (n = 2 of which 1 had rejected salvage therapy). Each patient's clinical course is presented in Figure 6E and Suppl. Table S4.

Multivariate analysis

To further assess the statistical significance of the identified clinical risk factors in DLBCL-SCNSL, we tested them in a multivariate analysis (Figure 7). For PFS, response to induction therapy and HDT-ASCT were significant prognostic factors ($P = 0.01$ and $P = 0.016$; Figure 7A). The proposed model of temporal stratification of DLBCL-SCNSL manifestation revealed a significance for CNS-POD6 ($P = 0.046$), but not for CNS-relapse ($P = 0.171$).

Investigating OS, response to induction therapy ($P = 0.041$) and completion of HDT-ASCT ($P = 0.023$) were identified as significant prognostic parameters. Also, the proposed temporal stratification reached significance for CNS-POD6 ($P = 0.004$), but not for CNS-relapse ($P = 0.081$; Figure 7B). Similar data were calculated for the whole cohort of SCNSL patients and are presented in Suppl. Figure S3.

DISCUSSION

Clinical management of SCNSL remains challenging. Open questions concern the best induction treatment, optimal consolidative therapy, and prognostic factors to guide therapeutic

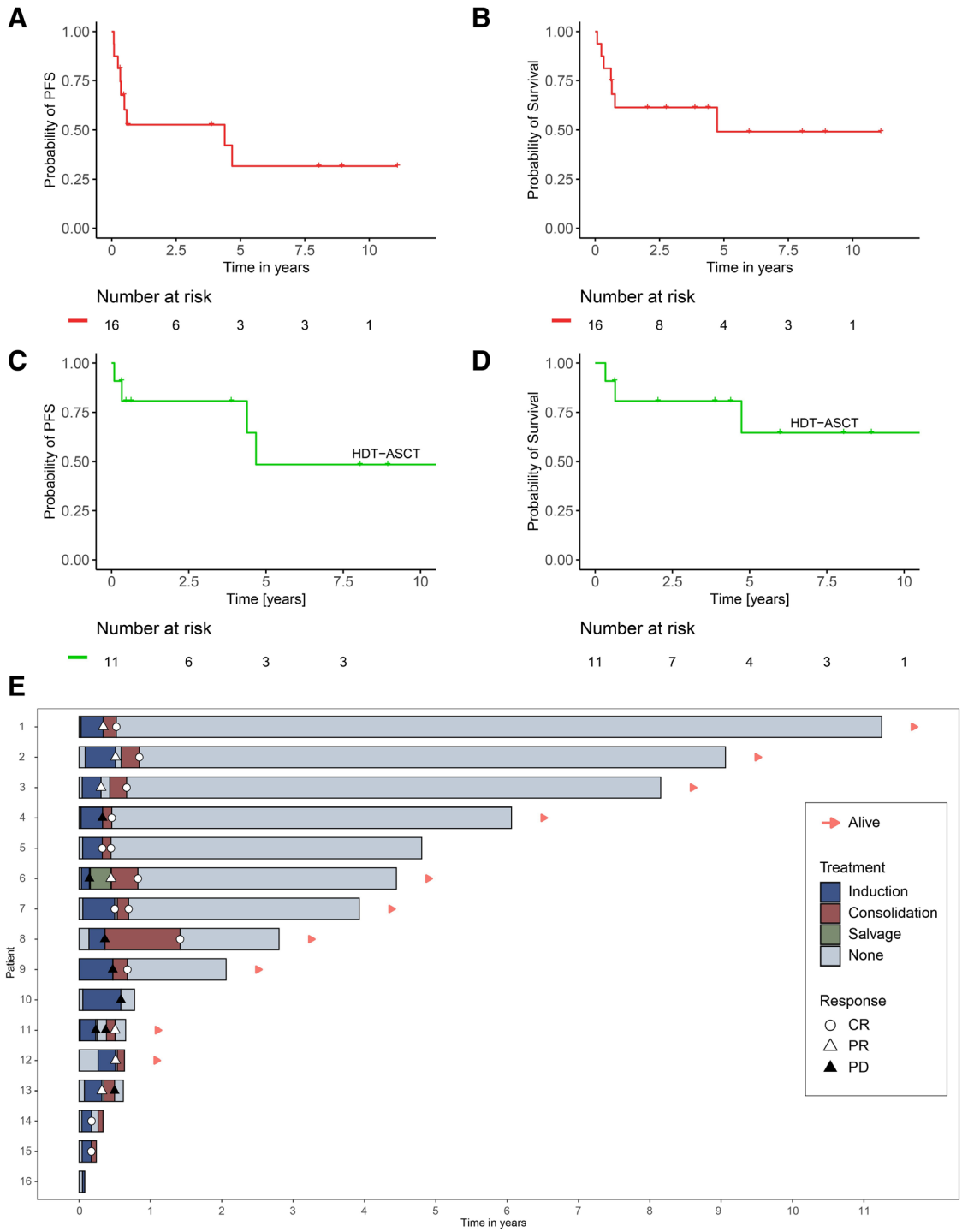

Figure 6. In-depth analysis of *de novo* DLBCL-SCNSL. Kaplan-Meier curves of *de novo* DLBCL-SCNSL; (A) PFS; (B) OS. Survival of *de novo* DLBCL-SCNSL patients receiving HDT-ASCT; (C) PFS; (D) OS. (E) Swimmer plot detailing the initial clinical course of every *de novo* DLBCL-SCNSL patient (see also Suppl. Table S4). DLBCL = diffuse large B-cell lymphoma; HDT-ASCT = high-dose chemotherapy and autologous stem cell transplantation; OS = overall survival; PFS = progression-free survival; SCNSL = secondary central nervous system lymphoma.

decisions. While significant progress has been made in the treatment of PCNSL including advanced clinical studies with an increasing role of HDT-ASCT, prospective trials for SCNSL are limited and optimal management has not been defined yet. Recently, position articles on SCNSL management have been published.[18,21] Hence, we conducted this retrospective real-world study of prognostic factors and long-term outcome in 124 SCNSL patients intensively treated in curative intention at 5 hematologic departments.

Overall, with a median follow-up of 50.7 months, the median 2- and 5-year OS rates for the predominant histologic subtype DLBCL-SCNSL patients in this real-world scenario were 43.3% and 33.5%, respectively. Despite differences in patient characteristics and treatment protocols, these results are comparable to reported prospective studies.

Specifically, four prospective phase 2 trials have been published to date.[10–13] In summary, these studies enrolled a maximum of 37 patients receiving HDT-ASCT.[10] The best 5-year OS rate in

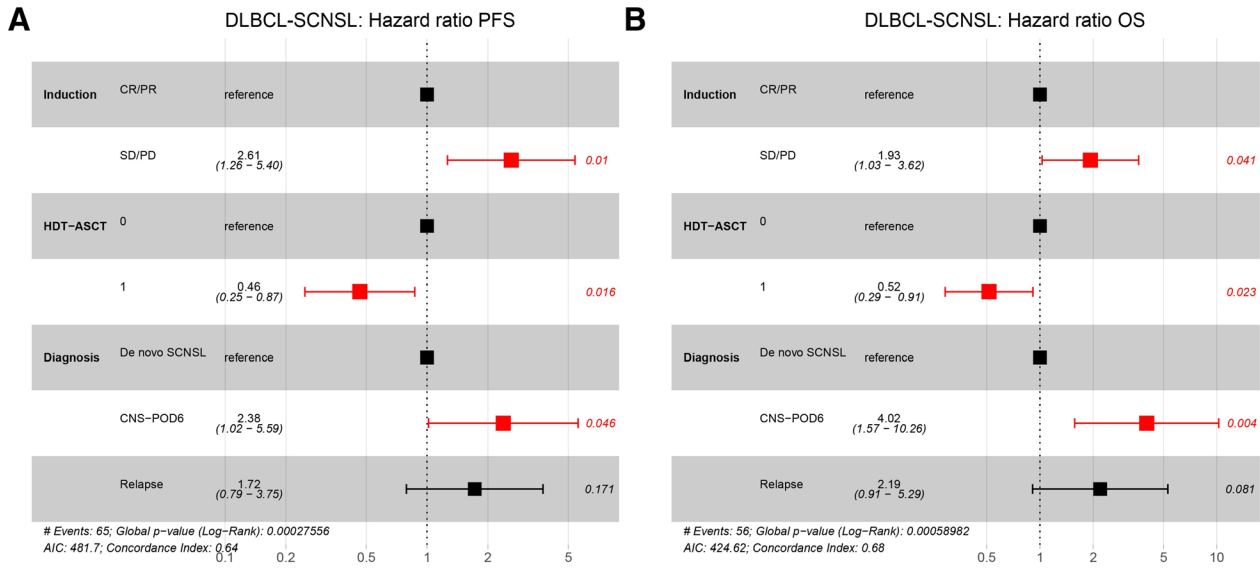

Figure 7. Multivariate analysis of prognostic factors in DLBCL-SCNSL. Forest plots of PFS (A) and OS (B) stratified by response to induction, HDT-ASCT, and temporal stratification (diagnosis of SCNSL). HDT-ASCT = high-dose chemotherapy and autologous stem cell transplantation; OS = overall survival; PFS = progression-free survival; SCNSL = secondary central nervous system lymphoma.

HDT-ASCT consolidated SCNSL patients was 68% in the Italian SCNSL1 trial.[11] In the largest prospective trial (MARIETTA), less than half of the study patients completed HDT-ASCT. These maximum treated patients exhibited a 2-year OS rate of 83% as compared with 46% for the total study population.[13]

One finding of our study emphasized the prognostic importance of early treatment response. Both, PFS and OS were significantly better in those patients who had achieved at least PR during induction. Indeed, 60.1% of our DLBCL-SCNSL patients with PR or CR after induction therapy survived 2 years compared with 25.4 % with SD or PD (5-year OS: 48.6% versus 16.7%; time-dependent cox $P < 0.001$).

This observation prompted us to evaluate whether differences in initial treatment responses and survival rates were explained by usage of different induction protocols. Most patients had been treated with HD-MTX, AraC, and partially TT with significant differences in drug composition and scheduling in the here analyzed real-world situation. In summary, PFS and OS were similar in DLBCL-SCNSL irrespective of the chosen induction protocol. A trend toward better OS was apparent in patients treated with MATRix followed by HDT-ASCT. Realizing small patient numbers in each group, cautious interpretation of these results is necessary. Nevertheless, one important question for future studies will be to evaluate the role of lymphoma autonomous and non-autonomous features of response.

Superior response rates have been observed in PCNSL patients treated within the randomized controlled IELSG trial. CR and PR rates of 49% and 37% were achieved in patients treated with MATRix.[8] Similar, excellent responses to MATRix have been reported in SCNSL patients, as recently published in the MARIETTA trial.[13] However, only 49% patients eventually completed HDT-ASCT: due to PD in 22, unsuccessful stem cells collection in 4, toxicity in 5, and other reasons in 7 patients. This suggests that further optimization of induction regimens for better lymphoma control, less toxicity, and facilitation of subsequent HDT-ASCT could support better outcomes for patients.

The most effective treatment strategy for PCNSL currently available is induction therapy including rituximab, MTX, AraC, and TT followed by HDT-ASCT or WBRT.[9] Excellent results for TT-based HDT-ASCT in 134 SCNSL patients with 3-year OS and PFS rates of 71.6% and 61.1% in an international retrospective analysis have been reported.[22] However, not all patients are eligible for intensive consolidation by myeloablative chemotherapy, and WBRT harbors the long-term risk of detrimental neurotoxicity.[9] In our retrospective study, 55.8% of those DLBCL-SCNSL patients who had completed HDT-ASCT survived at least 2 years as compared with only 17% without this consolidation. This observation underscores the pivotal role of HDT-ASCT as consolidation. Whenever feasible the ultimate treatment goal should be BCNU or busulfan-based myeloablative chemoimmunotherapy to optimize the chance of cure and to avoid neurotoxicity.

Elderly or frail patients with CNS lymphoma who cannot receive HDT-ASCT as consolidation require alternative consolidation or maintenance treatments. For example, lenalidomide has been investigated as maintenance therapy.[23] Also, procarbacine maintenance has been studied in the PRIMAIN trial and is now part of the PRIMA-CNS study.[24]

Another distinctive feature of our study cohort was administration of HDT-ASCT despite inadequate response including PD during induction treatment. This approach contradicts the exclusion of refractory SCNSL and PCNSL patients from HDT-ASCT in most CNS study protocols[8,10,12,13] and in current clinical practice for refractory/recurrent nodal aggressive lymphoma. In most of our refractory patients (13/18), the lymphoma status improved following HDT-ASCT. Intriguingly, prolonged OS above 4 years was observed in every third patient in this challenging situation. This encouraging result confirms similar findings in PCNSL patients, recently published by our group.[25] Hence, HDT-ASCT should be considered in initially refractory DLBCL-SCNSL in clinical routine and future studies, at least until alternative treatments such as targeted therapy or immunotherapies (e.g. CAR-T cell therapy) prove to be superior.

CNS involvement in systemic lymphoma at initial diagnosis is rare and management of this *de novo* SCNSL remains a matter of debate. In our cohort, 16 (13% of all) patients were diagnosed with *de novo* DLBCL-SCNSL. Eleven patients underwent HDT-ASCT and had an excellent prognosis with 65% long-term OS, while 4 patients without HDT-ASCT died within 1 year. The only long-term survivor not treated with HDT-ASCT had received CAR-T cell therapy. As reported previously, R-CHOP in addition to WBRT was insufficient because it did not improve

prognosis in CNS lymphoma patients.[26] However, the combination of anthracycline-based treatment such as R-CHOP and CNS-targeted induction represents the rational approach to eliminate lymphoma from both compartments.[13]

Overall, studies on *de novo* SCNSL are rare and mostly focus on the role of HDT-ASCT. A study from France demonstrated a significant survival benefit for patients receiving HDT-ASCT, and another study reported that patients with *de novo* SCNSL in CR after induction have an excellent prognosis after HDT-ASCT consolidation.[27,28] However, a study focusing on DLBCL-SCNSL in 44 patients could demonstrate no benefit of HDT-ASCT consolidation.[29] Despite these uncertainties, our data implicate that combinations of intensive CNS and systemically directed chemotherapies promise cure for a substantial proportion of SCNSL patients.

Strikingly, we were able to identify a hence not appreciated prognostic factor in SCNSL, the impact of temporal SCNSL occurrence in relation to initial diagnosis of systemic lymphoma. In contrast to *de novo* SCNSL, outcome of SCNSL with progression of lymphoma disease within 6 months (CNS-POD6) since initial treatment was particularly dismal. Median OS for DLBCL-SCNSL in the CNS-POD6 subgroup was 8.6 months as compared to 55.8 months in the *de novo* DLBCL-SCNSL and 17.3 months in CNS-relapse cases. In this cluster, we expect two group of patients: CNS-chemo-naïve patients with occult disease (which is not reached by R-CHOP-based treatment) and patients with primary refractory disease. However, we were unable to distinguish such groups based on peripheral lymphoma status. This may be due to the small sample size. Better molecular understanding will probably improve distinction of this patient groups. Notably, CNS-POD6 as prognosticator for OS was confirmed in multivariate analyses of both, the whole SCNSL cohort and DLBCL-SCNSL subgroup. Accordingly, we anticipate CNS-POD6 to pass confirmatory analyses within future studies.

The majority of CNS-POD6 patients in this real-world scenario had received maximum treatment intensity including HDT-ASCT and still exhibited a dismal outcome. This underlines the special need of new diagnostic avenues for early detection of CNS-POD6 patients and therapeutic approaches beyond classical chemoimmunotherapy and HDT-ASCT in this patient population. Thus, future studies should also consider the molecular heterogeneity of SCNSL as recently described in systemic DLBCL,[30–32] as it might be in marked contrast to the rather homogenous genetic landscape found in PCNSL.[33]

In conclusion, this study describes real-world management of 124 SCNSL patients in five German departments. The limitation our study includes its retrospective character and the heterogeneity of treatments among participating centers. Nevertheless, we were able to identify prognostic factors in SCNSL such as histopathology and initial treatment response. The importance of consolidation by CNS-directed HDT-ASCT was supported by favorable prognosis in accordingly treated patients. Notably, a fraction of patients not responding to induction therapy responded to HDT-ASCT and showed promising lymphoma control and OS. Patients with *de novo* DLBCL-SCNSL displayed a prognosis comparable to *de novo* systemic DLBCL, especially when managed including HDT-ASCT. Furthermore, temporal stratification of SCNSL and systemic lymphoma diagnosis revealed CNS-POD6 as a candidate prognosticator for future clinical and biological studies.

AUTHOR CONTRIBUTIONS

HT, VN-E, MW, DV, SS, TM, DM, VZ, RWK, LC, CIC, RS, and BC collected patient data. HT, VNE, NS, MW, CIC, MA, RS, and BC analyzed the data. HT, VNE, CIC, TF, LT, GI, GW, MA, SD, RS, and BC discussed the data and drafted the article. HT, VNE, RS, and BC wrote the article. All authors approved the final version and agreed to be accountable for all aspects.

DISCLOSURES

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