MATRix and HD-MTX/IFO/DEP treatment and autologous stem cell transplantation in secondary central nervous system lymphoma: a Dutch retrospective analysis

This Dutch retrospective study, conducted in multiple academic centers, evaluated the effectiveness and survival outcomes of two standard-of-care chemotherapy combinations for patients with secondary central nervous system diffuse large B-cell lymphoma (SCNS-DLBCL): high-dose methotrexate (HD-MTX), cytarabine, rituximab and thiotepa (MATRix) + autologous stem cell transplantation (ASCT) and HD-MTX, ifosfamide and liposomal cytarabine (HD-MTX/IFO/DEP) + ASCT (from the German NCT01148173 study) aiming to identify the more effective therapeutic strategy and improve treatment of SCNS-DLBCL patients.[1,2] This study showed that the MATRix regimen and ASCT consolidation are independently associated with a reduced risk of mortality in patients with SCNS-DLBCL. These data, together with the comparable non-relapsed mortality rates following MATRix+ASCT and HD-MTX/IFO/DEP+ASCT treatment, support MATRix as a favorable regimen in routine care of SCNS-DLBCL patients, but first need to be confirmed in additional studies.

SCNS-DLBCL is a rare and aggressive subtype of extranodal lymphoma. It is defined as an isolated central nervous system (CNS) relapse of systemic DLBCL (I-SCNS-DLBCL) or as CNS involvement concurrent with systemic DLBCL (C-SCNS-DLBCL).[3] Retrospective studies have shown poor outcomes with conventional chemotherapy, with a 2-year survival of 20%.[4,5] The survival rate rises to 40-60% in prospective trials, primarily attributed to consolidation with ASCT.[6] A recent prospective study, including 165 patients diagnosed with SCNS-DLBCL of whom 141 patients (85%) were treated with varying forms of HD-MTX-based treatment and 79 (48%) received ASCT, reported an adjusted hazard ratio of 0.31 for ASCT in SCNS-DLBCL in a multivariable Cox regression model.[7] Since no randomized trials exist for SCNS-DLBCL, current treatment recommendations primarily rely on four prospective trials supplemented by retrospective studies.[5,6] The earliest prospective SCNS lymphoma study evaluated HD-MTX/IFO/DEP and cytarabine, thiotepa and liposomal cytarabine followed by high-dose chemotherapy and ASCT, reporting a 2-year overall survival of 63%.[1] A second study reviewed HD-MTX and cytarabine followed by rituximab, cyclophosphamide, cytarabine and etoposide and ASCT, reporting a 5-year overall survival of 41%.[8] Thirdly, the effectivity of intrathecal rituximab/HD-MTX and rituximab combined with dexamethasone, cytarabine and cisplatin (R-DHAP) was assessed, showing a 1-year overall survival of 25%.[9] The fourth study evaluated the MATRix treatment followed by rituximab, ifosfamide, carboplatin and etoposide (R-ICE) to further limit systemic relapses and ASCT, reporting a 2-year overall survival of 46%.[10] This limited available evidence underscores the need for further research focused on evaluating SCNS-DLBCL treatment approaches.

MATRix induction consists of HD-MTX, cytarabine, rituximab and thiotepa (*Online Supplementary Table S1A*). The HD-MTX/IFO/DEP induction regimen combines HD-MTX, ifosfamide and liposomal cytarabine, followed by high-dose cytarabine, thiotepa and liposomal-cytarabine. Both regimens incorporate ASCT consolidation but differ in their conditioning protocols. In this study, MATRix induction treatment was followed by rituximab, carmustine (BCNU) and thiotepa conditioning based on the publication of Illerhaus *et al*. as opposed to the conditioning scheme without rituximab described in the IELSG32 publication by Ferreri *et al*.[11,12] The HD-MTX/IFO/DEP+ASCT regimen uses BCNU, thiotepa and etoposide. None of the patients in the MATRix+ASCT or HD-MTX/IFO/DEP+ASCT cohort received R-ICE treatment.

Inclusion criteria were: patients aged ≥18 years who were diagnosed between 2013 and 2024 with CNS localization of DLBCL as I-SCNS-DLBCL or C-SCNS-DLBCL and who initiated treatment with MATRix+ASCT or HD-MTX/IFO/DEP+ASCT. Diagnoses were based on histological biopsies or a combination of cerebrospinal fluid analysis and magnetic resonance imaging scans. Histological diagnoses were reviewed by expert hematopathologists (LMH, PMJ, AD, MAH, VT) according to the 4th WHO classification of lymphoid neoplasms.[13,14] In accord with the Declaration of Helsinki, this study was approved by formally constituted ethical committees of all participating centers with a waiver of informed consent (LUMC BRAIN-LYM study G20.126, October 2020).

Treatment response was assessed by magnetic resonance imaging of the brain and ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography scans. Treatment response was classified as complete (metabolic) response, partial response, and stable/progressive disease. Primary and secondary endpoints were overall survival (defined as the time from diagnosis until death from any cause), progression-free survival (defined as time until progression or relapse), and non-relapsed mortality. Best overall response rates of the CNS and systemic localizations were evaluated and combined into one best overall response rate in which the least favorable response was taken as the determining response after induction treatment and consolidation. Multivariable Cox proportional

Table 1. Summary of the patients' characteristics, outcomes and survival data for the cohort with secondary central nervous system diffuse large B-cell lymphoma (N=54).

Characteristics	All patients N=54	MATRix+ASCT N=21 (39%)	HD-MTX/IFO/DEP+ASCT N=33 (62%)	*P*
Age, years, median (range)	61 (36-75)	59 (36-74)	62 (38-75)	0.16
Age >60 years, N (%)	31 (57)	10 (48)	21 (64)	0.25
Male, N (%)	28 (52)	11 (52)	17 (52)	0.95
R-CHOP pre-treatment for systemic DLBCL, N (%)	46 (85)	16 (76)	30 (91)	0.14
Median lines of R-CHOP pre-treatment, N	6	4	6	0.81
Time from prior DLBCL to SCNS-DLBCL, N (%) Within 12 months Beyond 12 months	 25 (46) 29 (54)	 10 (48) 11 (52)	 15 (45) 18 (55)	0.88
Elevated LDH (>247 IU/L), N (%)	11 (20)	6 (29)	5 (15)	0.46
WHO status ≥2, N (%)	2 (4)	1 (5)	1 (3)	0.65
Subtype of SCNS-DLBCL, N (%) Concomitant Isolated	 29 (54) 25 (46)	 8 (38) 13 (62)	 21 (64) 12 (36)	0.07
Consolidation, N (%)	25 (46)	9 (43)	16 (48)	0.69
BORR after induction, N (%) Complete response Partial response Stable/progressive disease Died before response evaluation	 13 (24) 24 (44) 14 (26) 3 (6)	 9 (43) 8 (15) 2 (10) 2 (10)	 4 (12) 16 (48) 12 (36) 1 (3)	0.02
BORR after induction and consolidation, N (%) Complete response Partial response Stable/progressive disease Died before response evaluation	 20 (37) 18 (33) 13 (24) 3 (6)	 12 (57) 5 (9) 2 (10) 2 (10)	 8 (24) 13 (39) 11 (33) 1 (3)	0.03
Relapse after SCNS-DLBCL treatment, N (%) CNS only relapse Systemic only Both	33 (61) 13 (24) 10 (19) 10 (19)	10 (48) 5 (24) 2 (10) 3 (14)	23 (70) 8 (24) 8 (24) 7 (21)	0.63
Overall survival at 3 years, N (%) Alive Dead	 19 (35) 35 (65)	 11 (52) 10 (48)	 8 (24) 25 (76)	0.04
Cause of death, N (%) Disease-related Treatment-related	 27 (50) 8 (15)	 6 (29) 4 (19)	 21 (64) 4 (12)	0.13
Treatment-related deaths, N (%) Respiratory insufficiency Cardiac arrest Sepsis Neurotoxicity Bleeding	 2 (4) 2 (4) 2 (4) 1 (2) 1 (2)	 1 (2) 1 (2) 2 (4) - -	 1 (2) 1 (2) - 1 (2) 1 (2)	-
Median N of therapies	4	3	4	-

MATRix: high-dose methotrexate, cytarabine, rituximab and thiotepa; ASCT: autologous stem cell transplantation; HD-MTX/IFO/DEP: high-dose methotrexate, ifosfamide and liposomal cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone polychemotherapy; DLBCL: diffuse large B-cell lymphoma; SCNS-DLBCL: secondary central nervous system diffuse large B-cell lymphoma; LDH: lactate dehydrogenase; WHO: World Health Organization; BORR: best overall response rate; CNS: central nervous system.

hazard models were fitted to calculate hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) of prognostic variables. To correct for immortal time bias, multivariable models were fitted with consolidation as a time-dependent variable.

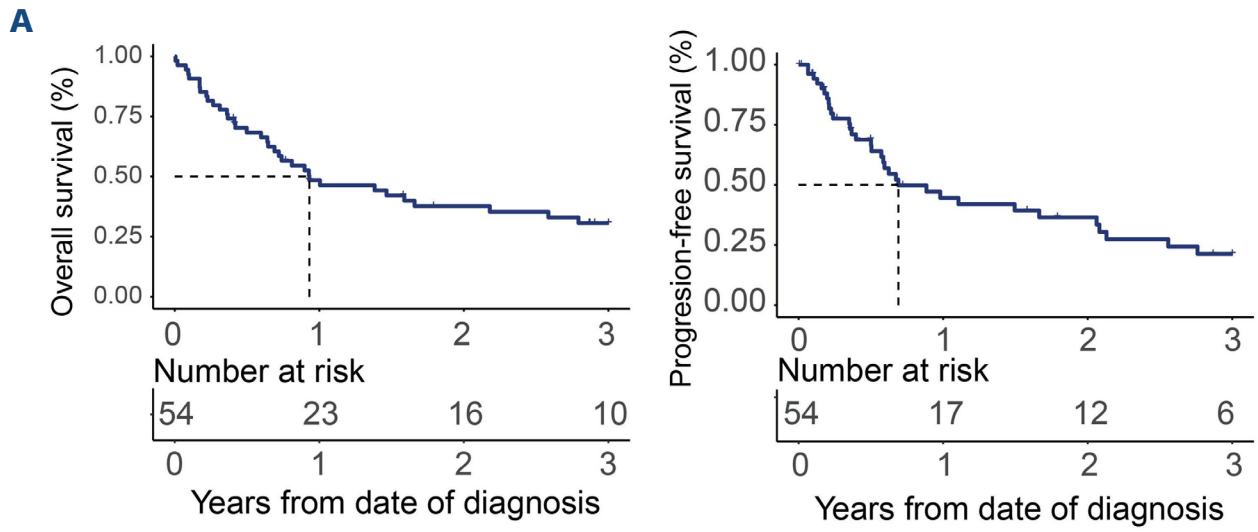
In total, 54 patients with SCNS-DLBCL were treated with either MATRix (N=21) or HD-MTX/IFO/DEP (N=33) induction treatment. The baseline characteristics of these two groups were similar (Table 1). Prior lines of therapy in relapsing patients are listed in *Online Supplementary Table S1B*. The median time from primary DLBCL diagnosis to SCNS-DLBCL was 13 months. Twenty-five patients (46%) had I-SCNS-DLBCL, relapse of systemic DLBCL, and 29 (54%) had C-SCNS-DLBCL, presenting with CNS and systemic localizations, of whom five (17%) were treatment-naïve and presented with *de novo* SCNS-DLBCL. Twenty-five patients (46%) underwent ASCT: 16 (48%) received induction therapy with the HD-MTX/IFO/DEP regimen, and nine patients (43%) with MATRix (*Online Supplementary Figure S1A*).

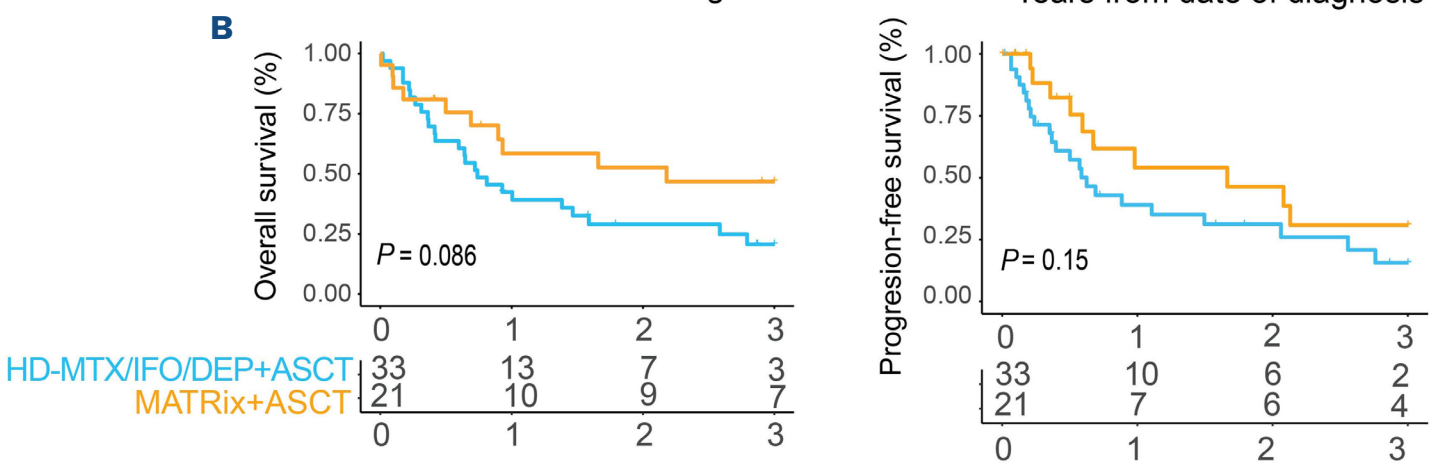
After induction treatment, 13 patients (24%) achieved a complete response, 24 (44%) a partial response, 14 patients (26%) had stable or progressive disease, and three patients (6%) died before response evaluation due to sepsis, cardiac failure, or an accident (Table 1, *Online Supplementary Figure S1B*). Three patients in the HD-MTX/IFO/DEP+ASCT group received rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) followed by HD-MTX chemotherapy (Figure 2) and two consecutive cytarabine-containing cycles. Patients on the MATRix+ASCT regimen had a better best overall response rate after induction and consolidation treatments than those on the HD-MTX/IFO/DEP+ASCT regimen (P=0.03) (Table 1), while both regimens had similar relapse rates (P=0.63) (Table 1). In total, ten patients (48%) treated with MATRix+ASCT experienced relapse after SCNS-DLBCL treatment, including five CNS-only relapses (24%), two systemic relapses (10%), and three relapses with both CNS and systemic involvement (14%). After HD-MTX/IFO/DEP+ASCT treatment, 23 patients (70%) experienced relapse: eight CNS-only relapses (24%), eight systemic relapses (24%), and seven relapses with both CNS and systemic involvement (21%).

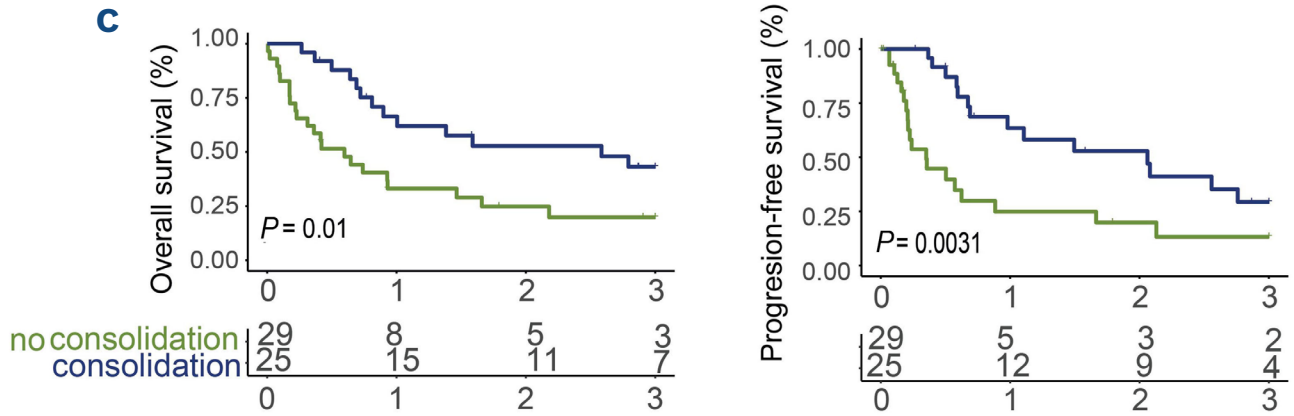
Six patients (29%) treated with MATRix+ASCT died of disease-related causes and four (19%) of treatment-related causes (respiratory insufficiency, cardiac arrest, and two from sepsis). Among the patients treated with the HD-MTX/IFO/DEP+ASCT regimen, 21 (64%) died of disease-related causes and four (12%) of treatment-related causes (respiratory insufficiency, cardiac arrest, neurotoxicity, and bleeding) (P=0.13) (Table 1).

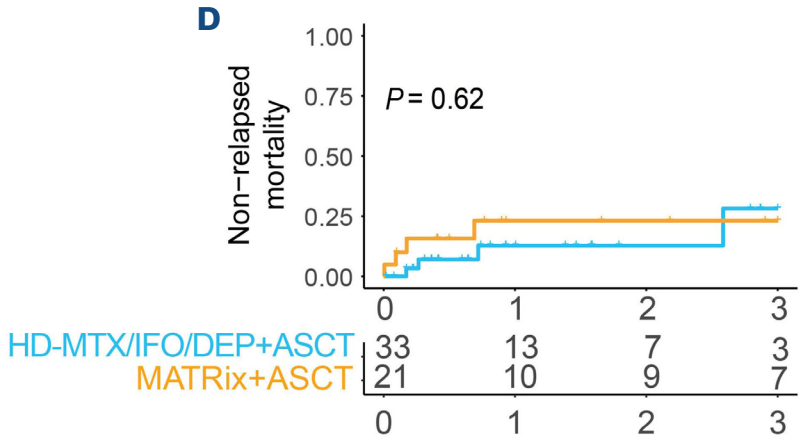
The median follow-up of this study was 10.2 months. The median overall survival was 11.2 months, being 26 and 9 months for the MATRix+ASCT and HD-MTX/IFO/DEP+ASCT cohorts, respectively (P=0.09) (Figure 1A, B). Likewise, the median progression-free survival was 8.3 months, being 20 and 7 months for the MATRix+ASCT-treated and HD-MTX/IFO/DEP+ASCT-treated patients, respectively (P=0.15) (Figure 1A, B). In a sensitivity analysis excluding treatment-naïve patients, the results remained similar (*data not shown*). No differences in survival were found between patients with parenchymal or leptomeningeal involvement at diagnosis (overall survival P=0.59, progression-free survival P=0.96) (*Online Supplementary Figure S2A*). In univariable analysis, patients with I-SCNS-DLBCL showed a favorable progression-free survival in comparison to those with C-SCNS-DLBCL (overall survival P=0.14, progression-free survival P=0.017) (*Online Supplementary Figure S2B*). In the group consolidated with ASCT, the median overall survival and progression-free survival were 31 and 25 months, respectively. Consolidation with ASCT significantly improved overall and progression-free survival compared to the survival outcomes of patients without ASCT consolidation (P=0.01 and P<0.01, respectively) (Figure 1C). However, this presents immortal time bias, as only patients who showed a favorable response were referred for consolidation. Similar treatment-related death rates and non-relapsed mortality were reported for recipients of the MATRix+ASCT (N=4, 19%) and HD-MTX/IFO/DEP+ASCT (N=4, 12%) regimens (P=0.62) (Figure 1D). To account for biases, a multivariable analysis was conducted demonstrating that both induction treatment with MATRix and subsequent consolidation with ASCT were independently associated with reduced risk of mortality (*Online Supplementary Figure S2C*). In addition, these effects for MATRix induction and ASCT consolidation were confirmed in a multivariable analysis with consolidation as a time-dependent variable to avoid immortal time bias (overall survival: MATRix induction HR=0.40 [95% CI: 0.21-0.79] P<0.01, ASCT: HR=0.37 [95% CI: 0.18-0.73] P<0.01; progression-free survival: MATRix induction HR=0.42 [95% CI: 0.20-0.87] P=0.02, ASCT HR=0.37 [95% CI: 0.17-0.79] P=0.01) (Figure 1E).

In the MATRix+ASCT group, five patients achieved complete responses after induction but did not proceed to ASCT because of deteriorating condition. Among them, two patients remained in complete response, one received radiotherapy consolidation, one was given rituximab, gemcitabine, dexamethasone and cisplatin for a systemic relapse, and one was not given any additional therapy. Three patients in partial response after MATRix induction did not undergo ASCT, one because of intracranial bleeding, one refused further treatment, and one was given lenalidomide as ASCT was not feasible due to the patient's condition. Two patients with stable or progressive disease after induction received palliative radiotherapy. Additionally, two patients initiated MATRix induction but died before response evaluation. In the HD-MTX/IFO/DEP+ASCT group, four patients with partial responses did not proceed to ASCT; two showed no clinical improvement, and two were unfit for ASCT. None received additional treatment. Among 12 patients with stable or progressive disease after induction, five received chimeric antigen receptor (CAR) T-cell treatment, one underwent









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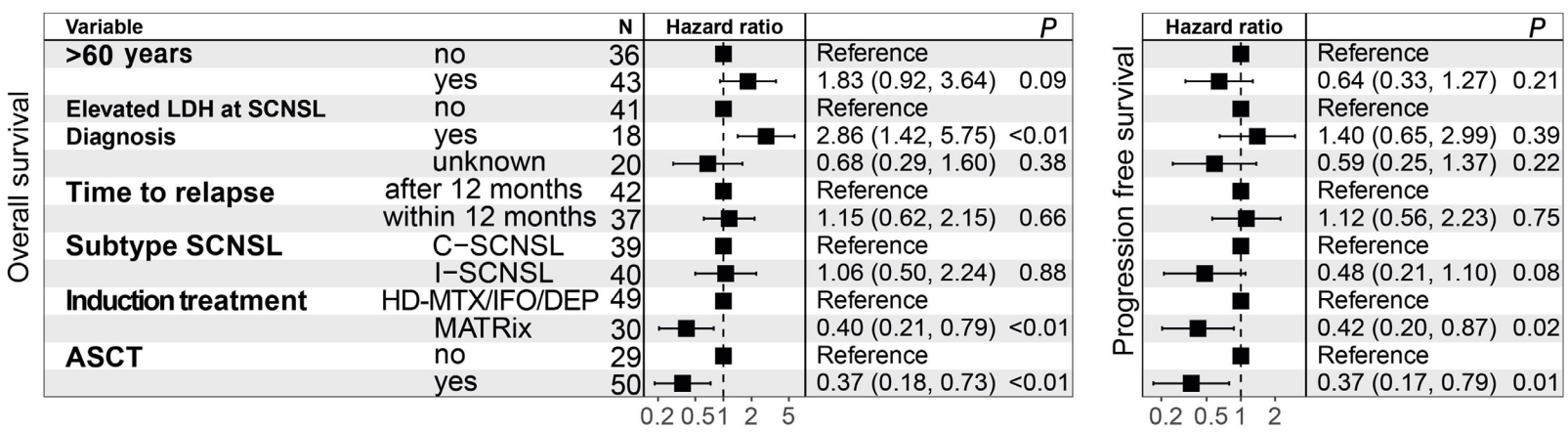

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Figure 1. Evaluation of survival outcomes following induction and autologous stem cell transplantation consolidation treatment and non-relapsed mortality analysis. (A) Progression-free survival (PFS) and overall survival (OS) of the complete cohort. (B) PFS and OS of patients treated with high-dose methotrexate, cytarabine, rituximab and thiotepa (MATRix) + autologous stem cell transplantation (ASCT) or high-dose methotrexate, ifosfamide and liposomal cytarabine (HD-MTX/IFO/DEP) + ASCT. (C) PFS and OS of patients who did or did not receive consolidation. (D) Non-relapsed mortality plot of patients treated with MATRix+ASCT or HD-MTX/IFO/DEP+ASCT. (E) OS and PFS Cox proportional hazards model including age, lactate dehydrogenase level at diagnosis, time to relapse, subtype of secondary central nervous system diffuse large B-cell lymphoma, induction treatment and ASCT consolidation with consolidation as a time-dependent variable. LDH: lactate dehydrogenase; SCNSL: secondary central nervous system lymphoma; C-SCNSL: concurrent central nervous system and systemic relapse of lymphoma; I-SCNSL: isolated central nervous system relapse of systemic lymphoma.

radiotherapy and six received best supportive care. One patient died before response evaluation. Relapsing patients received varying subsequent therapies, as no standard salvage regimen exists for SCNS-DLBCL.

Our study is the first to evaluate real-world data regarding two standard-of-care treatment options for SCNS-DLBCL patients: MATRix and HD-MTX/IFO/DEP induction treatment with the intention to consolidate with (rituximab), BCNU and thiotepa-conditioned ASCT. This enhances our understanding of treatment of SCNS-DLBCL and should be considered alongside other studies. However, outcomes may vary as patients enrolled in prospective studies tend to be younger and fitter and have fewer comorbidities, given the stricter selection criteria.

There are a few notable differences between the MATRix +ASCT and HD-MTX/IFO/DEP+ASCT regimens of this study. Firstly, the intended cumulative dose of HD-MTX in the MATRix+ASCT regimen is 14 g/m^2 while it is 8 g/m^2 in HD-MTX/IFO/DEP+ASCT. Secondly, rituximab, as an effective addition to CHOP treatment in DLBCL, is included in MATRix+ASCT treatment but absent in the HD-MTX/IFO/DEP+ASCT regimen.[15] Thirdly, previous studies reported that sequential exposure to HD-MTX followed by cytarabine, as utilized in the MATRix+ASCT regimen, produced synergistic effects in *in vitro* models.[16] We hypothesize that these could be potential explanations for the favorable association of MATRix+ASCT and survival outcomes. However, caution is needed in interpretation, as these are outcomes in a rare subtype of

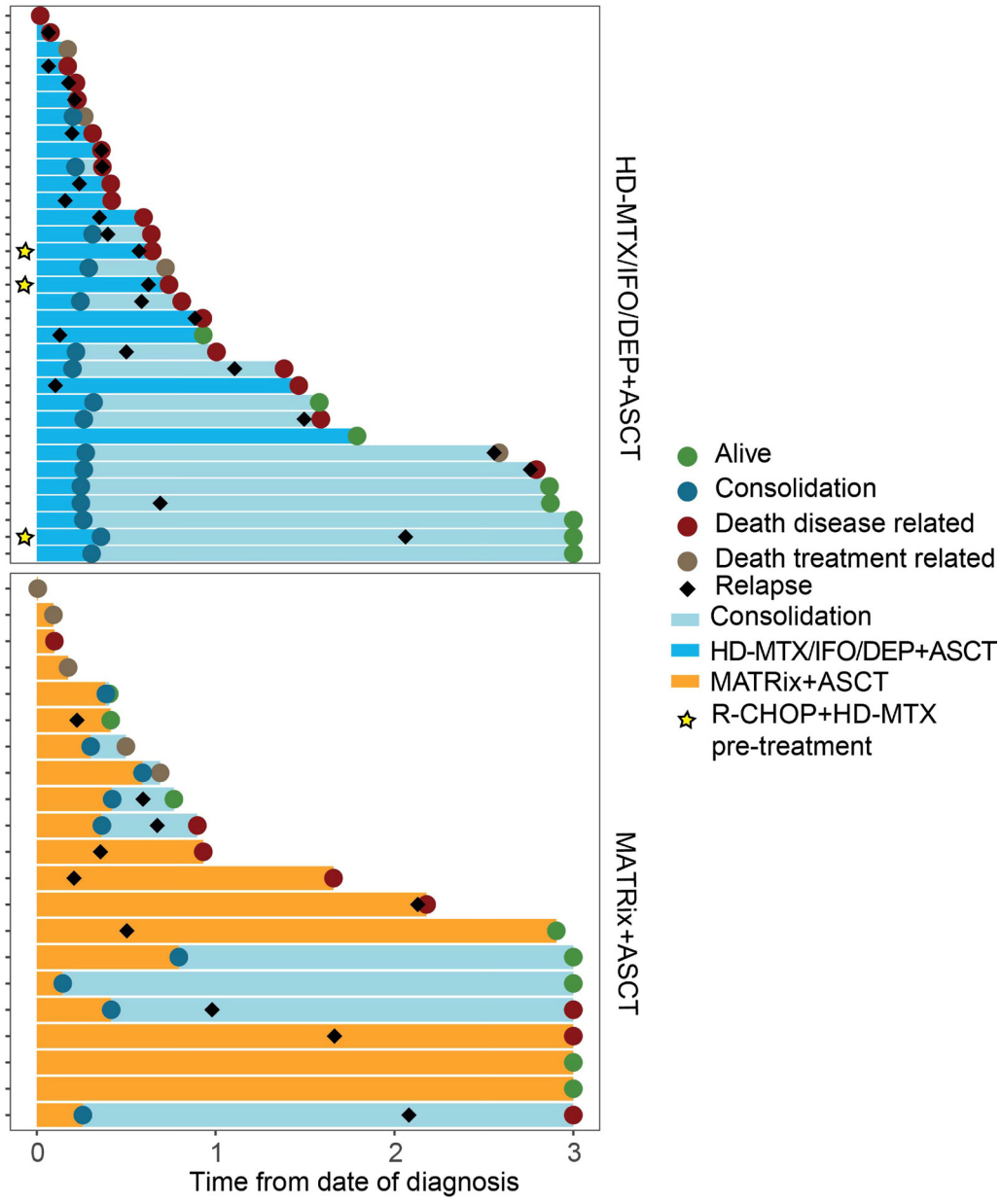

Figure 2. Swimmer plot of patients treated with high-dose methotrexate, ifosfamide and liposomal cytarabine + autologous stem cell transplantation or high-dose methotrexate, cytarabine, rituximab and thiotepa + autologous stem cell transplantation. HD-MTX/IFO/DEP+ASCT: high-dose methotrexate, ifosfamide, liposomal cytarabine + autologous stem cell transplantation; MATRix+ASCT: high-dose methotrexate, cytarabine, rituximab and thiotepa + autologous stem cell transplantation; R-CHOP+HD-MTX: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone + high-dose methotrexate.

DLBCL within a retrospective study with relatively small numbers. In our study 20 patients (37%) had systemic relapses; based on the MARIETTA trial, addition of R-ICE treatment after MATRix induction could be considered to lower the number of relapses.[10]

Our study has several limitations. As a retrospective analysis, selection bias cannot be entirely excluded, despite similar baseline characteristics of the two groups. Furthermore, the absence of standardized relapse protocols may have contributed to the varying outcomes. Patients with early progressive disease or relapse after DLBCL treatment may be eligible for emerging salvage therapies, such as CAR T-cell therapies. In our study five patients with stable or progressive disease after induction received CAR T-cell treatment, of whom only one achieved a durable remission. The four other patients all experienced systemic progression/relapse within 3 months. Three patients who relapsed after ASCT consolidation received CAR T-cell treatment and all three achieved complete response, however one patient died to a cardiac arrest, warranting further investigation. Emerging salvage therapies may have the potential to offer targeted, durable responses in this high-risk population.

While we recognize the inherent limitations of small cohort sizes and retrospective analyses, our findings offer valuable real-world insights into the treatment of SCNS-DLBCL, a rare and aggressive disease. This study complements prospective trials by reflecting the complexities and challenges of routine clinical practice, providing critical guidance for clinicians managing this population of high-risk patients.

Authors

Fleur A. de Groot,[1] Floriske G. Stedema,[2] Esther J. Kret,[1] Lorraine M. de Haan,[3] Patty M. Jansen,[3] Stefan Böhringer,[4] Arjan Diepstra,[5] Marjolein W.M. van der Poel,[6] Myrurgia Abdul Hamid,[7] Liane C.J. te Boome,[8] Valeska Terpstra,[9] Mirian Brink,[10] Hendrik Veelken,[1] Ruben A.L. de Groen,[1] Tim J.A. Dekker,[1] Marcel Nijland[2#] and Joost S.P. Vermaat[1#]

[1]Department of Hematology, Leiden University Medical Center, Leiden; [2]Department of Hematology, University of Groningen, University Medical Center Groningen, Groningen; [3]Department of Pathology, Leiden University Medical Center, Leiden; [4]Department of Biomedical Data Sciences and Department of Pharmacology and Toxicology, Leiden University Medical Center, Leiden; [5]Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, Groningen; [6]Department of Internal Medicine, Division of Hematology, GROW School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht; [7]Department of Pathology, Maastricht University Medical Center, Maastricht; [8]Department of Hematology, Haaglanden Medical Center, Den Haag; [9]Department of Pathology, Haaglanden Medical Center, Den Haag and [10]Department of Research and Development, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, the Netherlands

[#]MN and JSPV contributed equally as senior authors.

Correspondence:
J.S.P. VERMAAT - j.s.p.vermaat@lumc.nl

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Contributions

FAdG, JSPV and TJAD wrote the manuscript. SB and MB supported and deepened the statistical analyses. RALdG, LMdH, PMJ, MWMvdP, HV and MN contributed to the interpretation and translation of the results. FGS, LMdH, AD, VT, MWMvdP, MAH, VT and PMJ included patients. FGS, EJK, LCJtB, MWMvdP, MN and JSPV collected clinical data.

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