Pre-phase Rituximab and High-Dose Methotrexate Enables Reassessment of Intensive Treatment Eligibility in Frail Patients with CNS Lymphoma: A Multicenter Cohort Study

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Introduction

High-dose methotrexate (HD-MTX)-based induction followed by high-dose chemotherapy and autologous stem cell transplantation (HCT-ASCT) is the standard of care for patients with primary CNS lymphoma (PCNSL) and is also effective in secondary CNS lymphoma (SCNSL). However, many patients are deemed ineligible upfront due to age, poor performance status (PS), comorbidities, or prior therapies.

Aim

Expand accessibility to curative treatment options for frail and elderly CNS lymphoma patients by re-evaluation using a rituximab/high-dose methotrexate pre-phase.

Objectives

- Evaluate whether a pre-phase with rituximab and high-dose methotrexate (R-MTX) allows re-assessment of eligibility for intensive induction regimens in frail CNS lymphoma patients
- To determine the feasibility and safety of R-MTX as a bridging strategy prior to intensive treatment
- To explore the impact of frailty scoring and dynamic eligibility reassessment on survival outcomes

Methods

We conducted a multicenter retrospective study – key facts:

- 3 German academic centers 2017–2024
- 83 patients with PCNSL/SCNSL considered frail
- Therapy: Rituximab 375 mg/m² + HD-MTX ≥3 g/m² (renal-adjusted) Pre-Phase
- Patients Frailty Score (0–5): age, performance status, comorbidities, renal function, prior therapy
- Outcomes: feasibility, subsequent eligibility for intensive induction/HCT-ASCT, survival

Patient characteristics	n = 83
Age at diagnosis, median (range)	72 (35-84)
Female / Male, N (%)	38 (45%) / 45 (55%)
CNS lymphoma type, N (%)	
PCNSL	54 (65%)
rrPCNSL	7 (8%)
SCNSL	22 (27%)
Time to next treatment, days (range)	14 (7-35)

Table 1. Patient characteristics as indicated

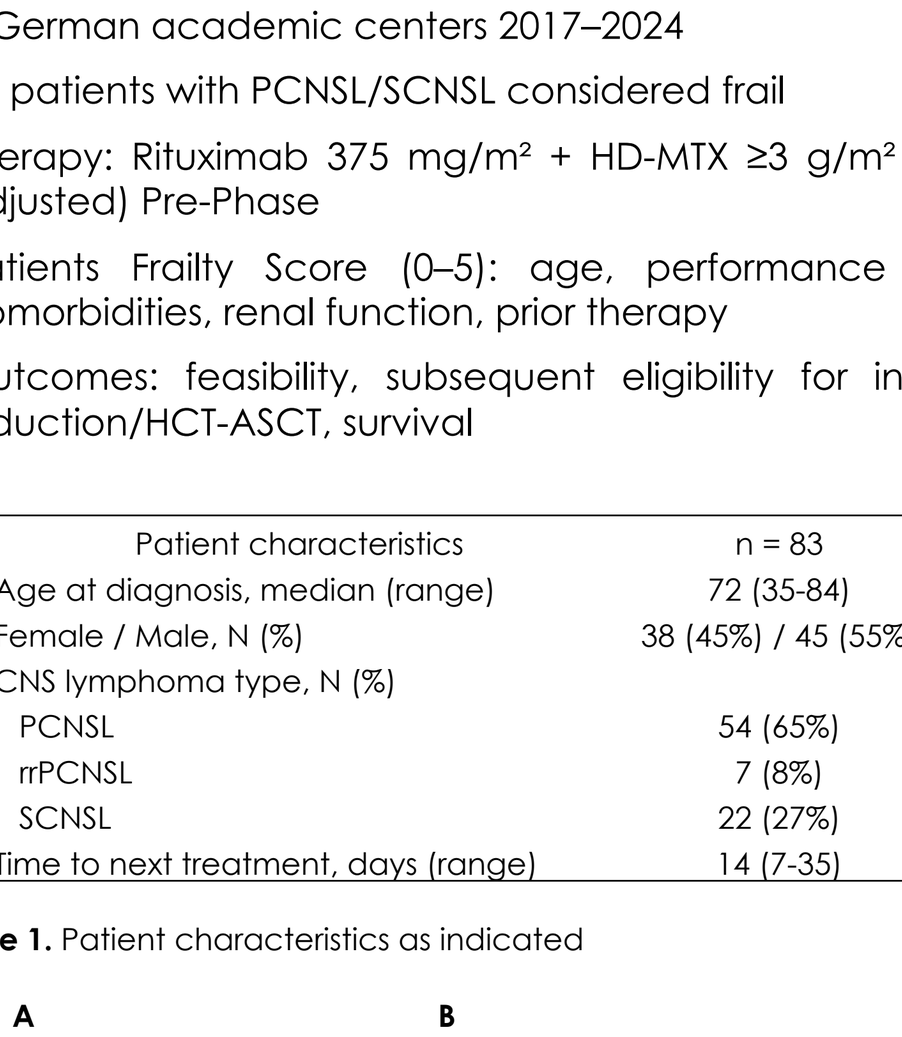


Figure 1. Patient characteristics regarding frailty
(A) Distribution of overall performance score (ECOG 0-4, n)
(B) Patients' age distribution (years, n)
(C) Distribution of Combined Frailty Score (CFS, n)
(D) Frequency of patients with indicated attributes (% of whole)

Results

- **58% (48/83)** proceeded to intensive induction (mainly MARTA/MATRix)
- **63% (30/48)** of those reached HCT-ASCT
- 34% received non-intensive therapy; 8% discontinued
- 4 patients initially non-intensive later reached HCT-ASCT

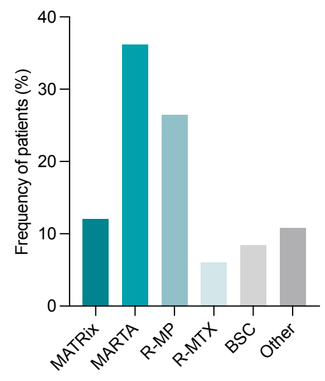


Figure 2. Treatment Regimens following R-MTX pre-phase treatment

- **Tolerable safety profile**
- No treatment-related deaths during R-MTX

Toxicity (CTCAE v5.0)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infection/ Infestation	2/83 (2 %)	1/83 (1 %)	5/83 (6 %)	4/83 (5 %)	1/83 (1 %)
Admission to ICU			3/83 (4 %)		
WBC decreased	15/83 (18 %)	4/83 (5 %)	5/83 (6 %)	1/83 (1 %)	0/83 (0 %)
Anemia	23/83 (28 %)	19/83 (23 %)	8/83 (10 %)	0/83 (0 %)	0/83 (0 %)
Platelets decreased	28/83 (34 %)	10/83 (12 %)	3/83 (4 %)	0/83 (0 %)	0/83 (0 %)
Hepatotoxicity	30/83 (36 %)	19/83 (23 %)	16/83 (19 %)	0/83 (0 %)	0/83 (0 %)
Acute kidney injury	10/83 (12 %)	5/83 (6 %)	0/83 (0 %)	0/83 (0 %)	0/83 (0 %)
Prolonged MTX clearance			14 (17 %)		

Table 2. Adverse Events as determined by CTCAE v.5.0)

- Low CFS and HCT-ASCT → **significantly better PFS & OS** (p=0.019 / 0.0004; p<0.0001)

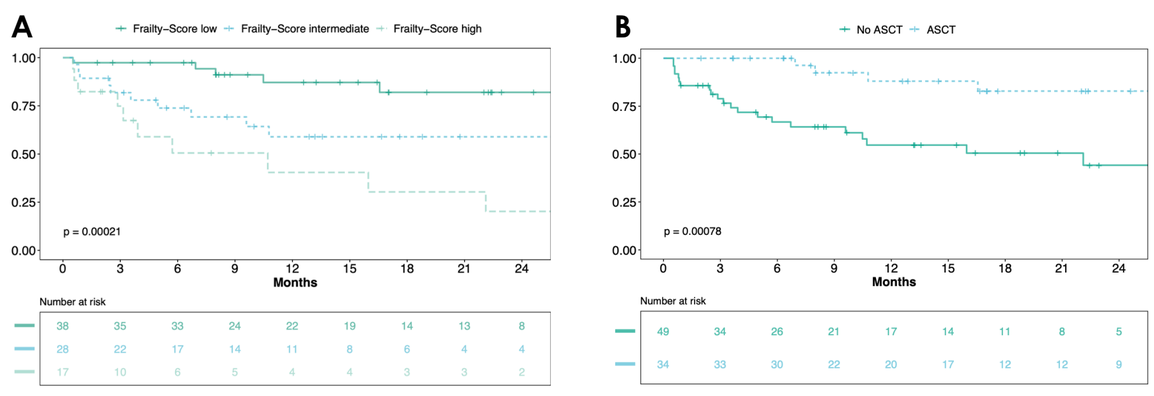


Figure 3. Overall Survival in dependence of CFS and ASCT
(A) Overall survival in dependence of CFS
(B) Overall survival in dependence of ASCT (yes/no)

Summary

- R-MTX pre-phase was safe with no treatment-related deaths, in an extensively frail cohort
- 58% proceeded to intensive induction; 41% ultimately underwent HCT-ASCT
- Pre-phase enabled reclassification of treatment eligibility
- Patients who reached HCT-ASCT had markedly superior survival outcomes
- This strategy offers a pragmatic approach to extend curative options in frail and elderly CNS lymphoma patients

Discussion

- Pre-phase R-MTX enables access to curative-intent therapy for patients otherwise deemed ineligible
- Dynamic re-assessment after R-MTX allows more patients to proceed to intensive regimens and HCT-ASCT
- This strategy may redefine standard of care for elderly and vulnerable CNS lymphoma patients; prospective trials are ongoing

References

Wendler J, Lewis RI, Kutilina A, Knott M, Isbell LK, Valk E, Borchmann P, Heger JM, Illerhaus G, Schorb E. *Pre-phase treatment with rituximab and high-dose methotrexate to re-evaluate eligibility for intensive induction treatment of frail patients with central nervous system lymphoma.* Haematologica 2025,doi: 10.3324/haematol.2024.286347

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