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PFS24 as a prognostic milestone in patients with newly diagnosed primary CNS lymphoma

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Abstract

High-dose chemotherapy followed by autologous hematopoietic stem cell transplantation has significantly improved overall survival (OS) in primary central nervous system lymphoma (PCNSL). However, early identification of long-term survivors remains a challenge. Progression-free survival at 24 months (PFS24) has emerged as a key prognostic marker in diffuse large B-cell lymphoma, but its relevance in PCNSL is still unclear. In this retrospective multicenter study, we analyzed data from 146 newly diagnosed, transplant-eligible PCNSL patients treated with MATRix-like regimens across 14 hospitals. With a median follow-up of 48 months, the 2-year PFS and OS rates were 50.4% and 65.6%, respectively. Of the 139 patients evaluable for PFS24-analysis, 51.1% reached PFS24, with a subsequent 5-year OS of 96.7%. Of note, the annual hazard rate for progression and death decreased to under 5% after 24 months, remaining stable thereafter. The patients who failed to reach PFS24 had a median OS of only 6.0 months. Key predictors of PFS failure included impaired Karnofsky performance status and treatment dose-reduction. In conclusion, PFS24 was identified as an important prognostic marker in PCNSL. Patients who achieve PFS24 have a favorable prognosis, whereas those who do not face poor outcomes and require innovative treatment approaches. This insight could aid in risk stratification and support the use of PFS24 as a surrogate endpoint in clinical trials.

Keywords Primary CNS lymphoma, PFS24, Overall survival

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To the Editor,

Induction immunochemotherapy followed by high-dose chemotherapy and autologous hematopoietic stem cell transplantation (HDC-AHSCT) has improved outcomes in primary central nervous system lymphoma (PCNSL), achieving a 7-year overall survival (OS) of > 50%. Therefore, HDC-AHSCT became the standard treatment for eligible patients [1–3]. However, strategies for early identification of long-term survivors are lacking. Achieving progression-free survival (PFS) at 24 months (PFS24) is an important milestone in diffuse large B-cell lymphoma (DLBCL) and correlates with OS comparable to the general population [4]. Also in patients with indolent B-cell lymphoma (i.e. follicular and marginal zone lymphoma) achieving PFS24 was shown to be associated with an excellent long-term outcome [5, 6]. The significance of PFS24 in PCNSL remains understudied. A recent meta-analysis indicated PFS as a surrogate endpoint for OS, but included limited HDC-AHSCT data and short follow-up (FU) [7]. The objective of the study was to evaluate the impact of PFS24 on OS in PCNSL patients and to identify of PFS24 failure (noPFS24).

We collected retrospective data on newly-diagnosed patients with PCNSL treated at 14 hospitals in 2 countries. Only patients who received MATRix-like regimens (MATRix, "Freiburg-protocol" and MARTA; see Supplementary Appendix) and were considered transplant-eligible were included. PFS24 was defined as being alive and free of relapse/progression within 24 months of treatment initiation. Details on patient selection and methodology are provided in the Supplementary Appendix.

Overall, 146 patients were included in the analysis (Supplementary Fig. S1). Baseline characteristics are shown in Table 1. Most patients (76.0%, $n = 111$) received MATRix induction, and ~ 60% ($n = 86$) underwent HDC-AHSCT. The main reasons for not undergoing HDC-ASCT included progression (43.3%, $n = 26$) and treatment-related toxicity ([TrT] 33.3%, $n = 20$). Median FU was 48 months (95% confidence interval [95%CI] 41.5–54.5), median OS was not reached. Two-year PFS was 50.4% (95%CI 42.1–58.7) and 2-year OS was 65.6% (95%CI 57.9–73.3). There were 75 events (92% [$n = 69$] occurred within 24 months) and 52 patients (35.6%) died. The annual hazard rate for progression and death was highest within the first 12 months (26.3% and 13.8%, respectively) and decreased to < 5% after 24 months and remained at this level at subsequent time-points (Fig. 1A). This confirmed PFS24 represents a critical benchmark for further evaluation.

Table 1 Patients' characteristics

	Whole cohort ($n = 146$)		PFS24 cohort ($n = 70$, 50.4%)		noPFS24 cohort ($n = 69$, 49.6%)		*p* value
	n	%	n	%	n	%	
Age, median (range)	60 (24–83)		60.5 (24–83)		61 (34–77)		0.41
> 65 years	27	18.5	12	17.1	14	20.2	0.67
Sex, male	86	58.9	41	58.5	41	59.4	0.53
Karnofsky PS < 70%	40	27.4	14	20.0	25	36.2	**< 0.03**
Elevated LDH	67	47.9	30	43.4	36	54.5	0.15
n/a	6		1		3		
Elevated CSF protein	78	76.5	40	69.0	35	83.3	0.16
n/a	44		12		37		
DBS	89	60.1	44	62.8	39	56.5	0.49
ALC < 875/µL	30	22.7	9	14.3	20	31.2	**0.03**
n/a	14		7		5		
High risk 3 F score	17	12.9	3	4.8	14	21.9	**< 0.01**
n/a	14		7		5		
High risk IELSG score	30	29.1	19	33.3	14	29.2	0.83
n/a	45		13		30		
Dose reduction	70	49.6	27	38.6	37	57.8	**0.04**
n/a	5				5		
Treatment							0.27
- MATRix	111	76.0	52	78.3	54	80.8	
- Freiburg protocol	20	13.7	12	14.5	6	7.7	
- MARTA	15	10.3	6	7.2	9	11.5	
HDC-AHSCT	86	58.9	53	72.3	26	35.9	**< 0.001**

Abbreviations ALC, absolute lymphocyte count; CSF, cerebrospinal fluid; DBS, deep brain structures; LDH, lactate dehydrogenase; HDC-AHSCT, high-dose chemotherapy and autologous stem cell transplantation; IELSG score: International Extranodal Lymphoma Study Group score; n/a, not available; noPFS24, no progression-free survival at 24 months; PFS24, progression-free survival at 24 months; PS, performance status; 3 F score: Three-factor prognostic score

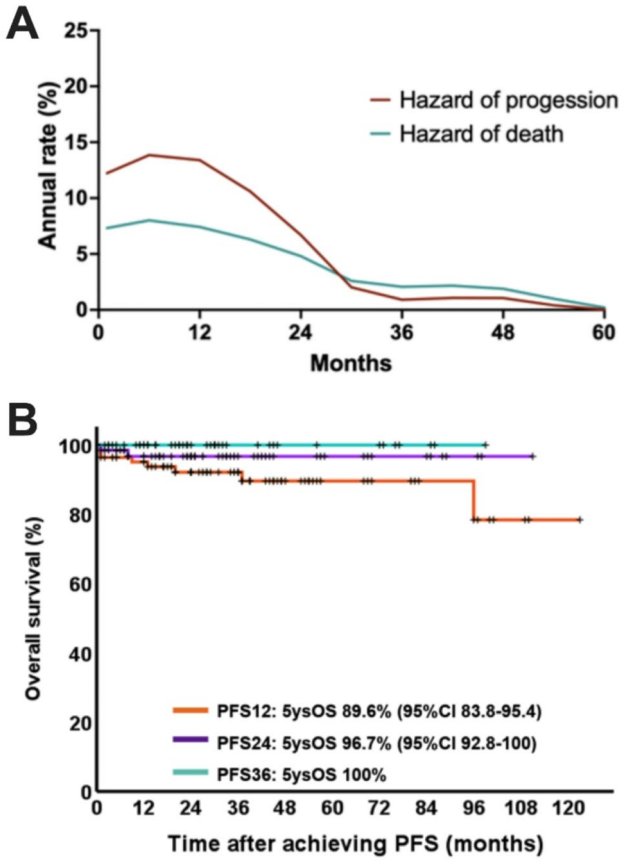

Fig. 1 Risk of relapse and/or death in fit patients diagnosed with PCNSL over time. (**A**) Smoothed hazard plots of death and progression over time. (**B**) Overall survival (OS) according to progression-free survival (PFS) time-points (PFS12, PFS24, PFS36)

A total of 139 patients with sufficient FU were evaluable for PFS24 analysis, of which 70 (51.1%) achieved PFS24. In the noPFS24 cohort, 23 patients had refractory disease (33.3%), and 11 patients (15.9%) died due to TrT. Salvage therapies (data available in 65.6% patients, $n = 38$) included mainly radiotherapy (36.8% patients) with/without systemic therapy (i.e. ibrutnib, temsirolimus or temozolomide) and high-dose methotrexate-based chemotherapy (36.8% patients). About 21.0% of patients received best supportive care (BSC) only. Interestingly, 29% of patients ($n = 17$) in the PFS24 cohort did not undergo HDC-AHSCT yet still were able to achieve a good long term outcome. Almost half of these patient (47.1%, $n = 8$) needed dose reduction. None of them had a high-risk disease according to three-factor prognostic score [8]. Multivariate regression analysis confirmed that impaired Karnofsky performance status (hazard ratio [HR]: 3.95 [95%CI 1.4–11.2]) and dose reduction (HR: 2.93 [95%CI 1.1–7.8]) were associated with noPFS24 (univariate regression analysis was shown in **Supplementary Tab. S1**). The 5-year OS after achieving PFS24 was 96.7% (95%CI 92.8–100). Conversely, subsequent median OS (after progress/recurrence) for noPFS24 was 6.0 months (95%CI 0-12.4) (**Supplementary Fig. S2**). Landmark-analysis at other time-points (i.e., PFS at 12 and 36 months) showed that subsequent 5-year OS increased continuously with only a small difference beyond PFS24 thereby, reaching a plateau (Fig. 1B).

Our data show that PFS24 is a prognostic milestone for fit patients with PCNSL treated with current standard therapies. Consistent with data in systemic DLBCL [4], patients with PCNSL, who achieve PFS24 have an excellent prognosis with a 5-year OS of 96.7%. The rate of progression/death decreased to < 5% after 24 months and remains stable, underscoring the prognostic value of PFS24 for long-term OS. This is important information for patient counseling, FU planning, and future clinical trials.

On the other hand, patients not achieving PFS24 have a very poor prognosis. Two important aspects should be considered. First, this group includes patients who are primary refractory/experience early relapse, indicating chemorefractoriness. Data from the French LOC network previously showed that patients with early relapse (< 12 months) have a dismal outcome (median subsequent OS < 5 months), with almost one-third receiving only BSC care [8]. In contrast to this registry, our cohort consists of patients a priori selected for intensive approaches, suggesting eligibility for potential salvage therapies. However, radiation and non-cross-resistant chemotherapy have limited efficacy [9]. Recently, CD19-targeted CAR T-cell therapy has shown promising results in these difficult-to-treat patients [10, 11]. Second, an important issue is TrT, which can lead to treatment discontinuation or even death [12]. A subset of our patients, none of whom were high-risk, achieved PFS24 without proceeding to HDC-AHSCT, suggesting that selected patients may benefit from treatment de-escalation. However, due to the small sample size, these findings should be interpreted with caution. Whether treatment de-escalation could minimize toxicity while maintaining efficacy is currently under investigation.

The limitations of our study are its retrospective nature, resulting in selection bias (possibly not including all patients eligible for intensified treatment), and partially incomplete FU (excluding some patients with ongoing response) as well as lack of heterogeneity in induction treatment. Our data should be validated in an independent cohort, particularly in patients treated with induction regimens other than MATRIx-like.

Taken together, PFS24 is a valuable predictor of long-term outcomes in patients with newly diagnosed PCNSL, enabling effective patient risk stratification, and serving as a surrogate endpoint in clinical trials to expedite treatment evaluation and benchmark new therapies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13045-025-01700-7.

Supplementary Material 1

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Author contributions
V.Z. collected, analyzed and interpreted the data, and wrote the paper. T.R.H. reviewed, and revised the paper, H.M.W. collected and analyzed the data and revised the paper, L.A., S.A.B., G.B., B.J., C.K., C.L., J.P., S.P., M.P.S., J.S., U.S., A.S., T.P.V., J.W., collected the data and reviewed. D.M. interpreted the data and reviewed the paper. All authors approved the final version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
All procedures were performed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study was carried out after approval of the Medical Faculty of the Otto von Guericke University Magdeburg, Magdeburg, Germany (approval no. 18/22).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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