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Elderly long-term survivors in the Nordic phase II study with first-line maintenance temozolomide for primary central nervous system lymphoma: a 10-year follow-up

Primary central nervous system lymphoma (PCNSL) is a separate group of lymphomas confined to the central nervous system (CNS) including the eyes. More than 95% of the cases represent aggressive CD20⁺ diffuse large B-cell lymphoma (DLBCL) with distinct clinical and biological features and poor prognosis.¹

The outcome of PCNSL is particularly poor among elderly patients, and the improvements achieved in survival during recent decades appear to be restricted to younger PCNSL patients.^{2,3} The main feature of our Nordic phase II PCNSL study was its focus on elderly patients. The treatment for the elderly subgroup in our study consisted of de-escalated induction immunochemotherapy followed by maintenance temozolomide. We have previously reported the 22-month results with 2-year overall survival (OS) rates of 60.7% and 55.6% ($P=0.40$) and progression-free survival (PFS) rates of 33.1% and 44.4% ($P=0.74$), among younger and elderly patients, respectively.⁴ In our study, we found an astonishing good result for the elderly patients with a median duration of response (DOR) not reached among elderly patients, compared to a median DOR of 10 months among younger patients treated with more intensive immunochemotherapy but without maintenance temozolomide. One of our hypotheses is that the improved results among the elderly subgroup were due to maintenance temozolomide therapy. In PCNSL, late relapses occur but long-term follow-up data is scarce. Herein, we present long-term outcomes and neurocognitive performance at 10 years after diagnosis in the Nordic phase II first-line PCNSL study (*clinicaltrials.gov. Identifier: 01458730*).

In this prospective multicenter phase II study, immunocompetent, newly diagnosed, and histologically confirmed PCNSL patients up to 75 years of age at diagnosis were treated with an age-adjusted multi-agent immunochemotherapy regimen. The induction regimen for the younger subgroup (18-65 years at diagnosis) included high-dose methotrexate (HD-MTX) and HD-cytarabine combined with rituximab, ifosfamide, cyclophosphamide, dexamethasone, intrathecally administered liposomal cytarabine, vindesine, and vincristine. In the de-escalated induction regimen for the elderly subgroup (66-75 years at diagnosis), cyclophosphamide and vincristine were replaced with temozolomide, followed by temozolomide maintenance in patients responding to induction therapy.⁴

For baseline evaluation, response assessment, and statistical design, see the original article.⁴ All patients were intended to be followed for 120 months after the end of treatment, which

in the younger subgroup was the end of induction therapy and, in the elderly subgroup, was the end of maintenance therapy. Patients with refractory disease, progressive disease (PD), and patients not achieving a complete response (CR) at the end of planned therapy went off-study and were followed for OS only. OS, PFS, and DOR were estimated by using the Kaplan-Meier method. Crude differences between the groups of patients were tested using the log-rank test. Median follow-up was calculated using the reverse Kaplan-Meier method.

The study was approved by the local ethics committees and conducted in agreement with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Sixty-six patients (35 males and 31 females) from 12 centers in Denmark, Norway, Sweden, and Finland were enrolled between May 2007 and October 2010. Baseline characteristics, treatment, responses, and adverse events have been previously reported.⁴ The overall response rate was 73.8% for the entire cohort, 69.9% in the younger and 80.8% in the elderly subgroup. Myelosuppression after HD-cytarabine cycles was the most common grade 3-4 adverse event.

After a median follow-up of 10 years, the 10-year OS rate was 29.8% (95% confidence interval [CI]: 20.5-43.4), the 10-year PFS rate was 13.3% (95% CI: 6.6-26.8), and median DOR was 13.2 months (95% CI: 7.7-72.4) for the entire cohort. Among the younger patients, the 10-year OS rate was 30.4% (95% CI: 18.8-49.1), and the 10-year PFS rate was 8.5% (95% CI: 2.6-27.8). Likewise, the 10-year OS rate was 29.6% (95% CI: 16.6-53.0), and the 10-year PFS rate was 21.3% (95% CI: 8.6-46.9), for the elderly patients. Median PFS was 13 months for the entire cohort (range, 1,2-162,8 months), 11 months in the younger (range, 1.8-168.5 months), and 57 months (range, 0-140 months) in the elderly subgroups (Figure 1).

Seventeen of 66 patients (25.8%) were known to be alive at 10 years after diagnosis. Long-term survivors were three younger male patients, eight younger female patients, two elderly male patients, and four elderly female patients. Seven patients had primary refractory disease, six younger patients, and one elderly patient. Early relapses less than 1 year after the end of treatment were observed in 21 patients. Of these, 13 patients belonged to the younger subgroup. Later relapse occurred in 14 patients, at 15-168 months after the completion of therapy.

The number of deaths at the end of the study was 46 (69.7% of the 66 patients enrolled), and three patients were lost to follow-up at around 8 years. The cause of death was PCNSL in 25 patients. Four patients (6%) aged 64, 66, 73, and 74

years at diagnosis experienced treatment-related death due to neutropenia and sepsis-induced multi-organ failure,

all after the first HD-cytarabine dose. The cause of death was either unknown or not indicated in 14 patients. In the

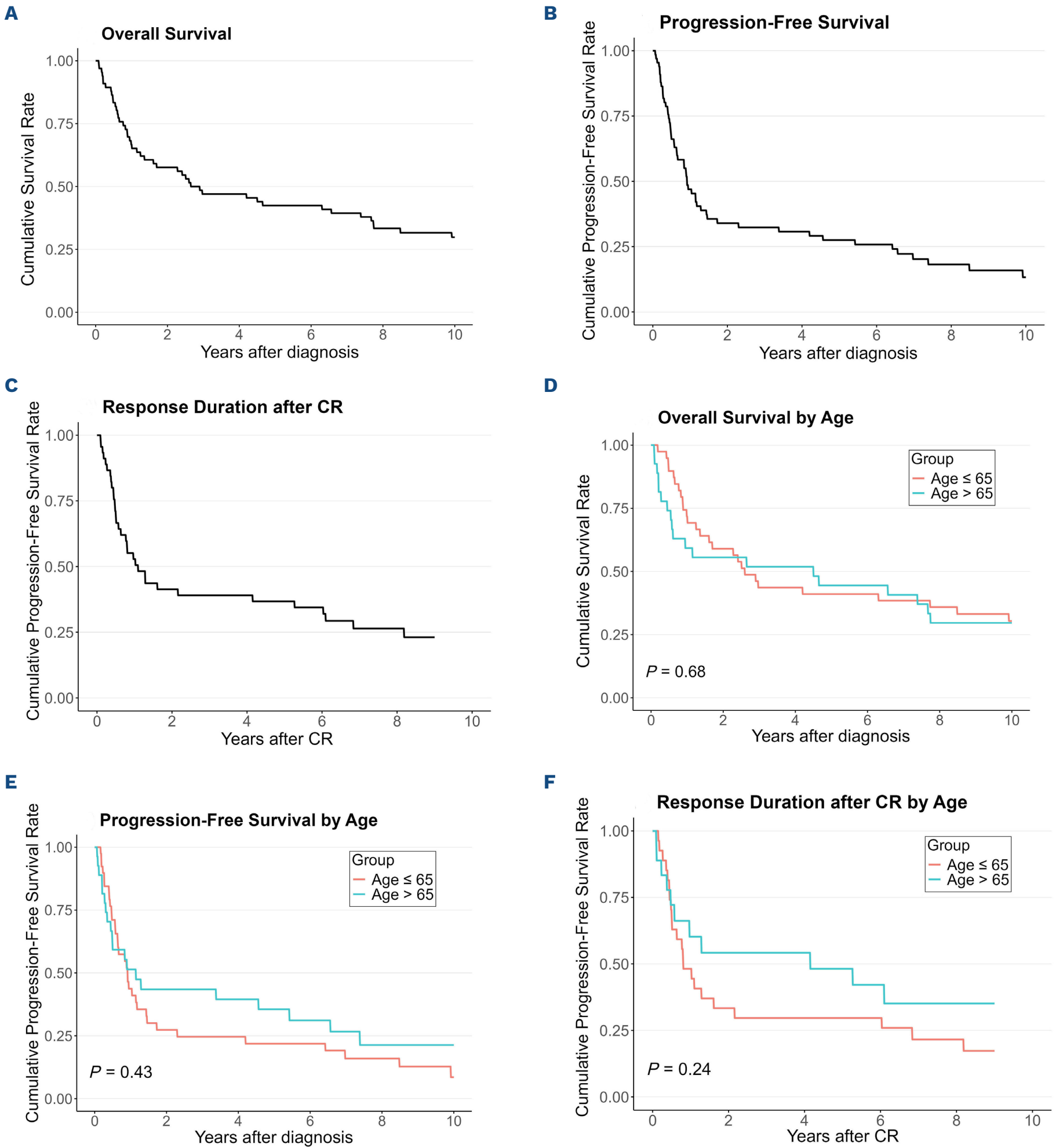


Figure 1. Overall survival, progression-free survival, and duration of response after complete remission. Long-term survival of patients and duration of complete remissions (CR). Demonstrative Kaplan-Meier curves depict (A) overall survival in the entire study population, (B) progression-free survival in the entire study population, (C) duration of response in the entire study population and differences in overall survival, progression-free survival, and duration of response between elderly and younger subgroups (D, E, and F, respectively).

remaining three cases, the cause of death was general deterioration, second malignancy, and neurotoxicity after radiotherapy at relapse.

In the entire study population, Eastern Cooperative Oncology Group performance score (ECOG PS), mini-mental state examination (MMSE), and functional independence measure (FIM) improved or remained unchanged in the majority of the patients with similar results among long-term survivors. For the long-term survivors, patient characteristics, ECOG PS, neurocognition, number, and localization of tumor(s) at diagnosis and relapse are shown in Table 1.

Here, we report the long-term results of the Nordic phase II study on newly diagnosed PCNSL patients treated with a multiagent immunochemotherapy and a de-escalated induction regimen followed by temozolomide maintenance only for elderly patients. In this study, we found a significant proportion of elderly long-term survivors, with a 10-year OS rate of 29.8%. We also report the improvement in both neurocognitive status as well as functional independence of the patients treated in our study.

With the longest follow-up among all published randomized trials in PCNSL, Ferreri *et al.*⁶ have reported a 7-year OS rate of 70% with a median follow-up of 88 months in

patients treated in IELSG32 trial with MATRix followed by consolidation therapy. However, elderly patients (age 66-70 years at diagnosis) were eligible for that trial only if their PS was considerably good (ECOG PS 2 or less) whereas in our study, patients up to the age of 75 years at diagnosis were eligible for the trial also in poor PS (ECOG PS 0-4). Moreover, 44% of the patients in our elderly subgroup were older than 70 years at diagnosis and 26% of the patients had a poor PS (ECOG PS 3-4) leading it impossible to compare the results of these two studies.

The intergroup ANOCEF-GOELAMS study published by Omuro *et al.*⁷ was the first randomized trial specifically designed for elderly PCNSL patients. In that study, two different HD-MTX-based regimens were studied with one of the regimens containing temozolomide, which was also a part of the regimen for elderly patients in our study. In ANOCEF-GOELAMS, 48 patients were assigned to the MTX-temozolomide arm, with a 2-year OS rate of 39% in this group but no long-term follow-up data published. In our study, the 2-year OS rate for elderly patients was notably higher, 55.6%.⁴

Two phase II studies including elderly PCNSL patients have published long-term results with 10-year follow-up data.^{8,9}

Table 1. Patient characteristics, Eastern Cooperative Oncology Group performance score, neurocognitive data, number and localization of the tumor, localization of tumor at relapse for the confirmed long-term survivors.

Patient number	Age in years at inclusion	Sex	ECOG PS change during follow-up	MMSE change during follow-up	FIM change during follow-up	Single tumor	Multiple tumors	Deep structures involved	Relapse	Previously involved region at relapse
1	52	F	→	↑	→	1	-	No	No	-
2	66	F	↑	↑	↑	-	1	Yes	No	-
3	64	F	↑	→	↑	-	1	No	Yes	Yes
4	58	M	→	↑	→	-	1	Yes	No	-
5	64	F	→	→	NA	1	-	Yes	Yes	Yes
6	50	F	→	↑	→	-	1	No	Yes	Yes
7	52	F	↑	↑	↑	1	-	Yes	No	-
8	55	F	↑	NA	NA	-	1	Yes	Yes	NA
9	66	F	↑	↑	↑	-	1	Yes	No	-
10	68	F	→	↑	↓	1	-	Yes	No	-
11	50	F	↑	↑	↑	1	-	No	Yes	NA
12	71	M	→	↑	↑	-	1	Yes	Yes	No
13	50	F	NA	NA	NA	-	1	No	No	-
14	40	M	→	NA	NA	1	-	No	Yes	NA
15	69	F	→	→	→	-	1	No	No	-
16	63	M	→	NA	↑	1	-	Yes	No	-
17	66	M	↓	↓	↑	-	1	Yes	No	-

F: female; M: Male; ECOG PS: Eastern Cooperative Oncology Group performance score; MMSE: mini-mental state examination; FIM: functional independence measure; →: unchanged; ↑: improved; ↓: declined; NA: not applicable.

Seidel *et al.*⁸ reported a Bonn group's study with a 10-year OS rate of 9% in patients above 60 years of age at diagnosis whereas there were no long-term survivors at 10 years in the other phase II trial MATILDE reported by Ferreri *et al.*⁹ Compared to these results, the long-term survival of elderly patients in our trial is significantly higher. With the median OS of 33.3 months among elderly patients in our study, the results remain more favorable also compared to other studies specifically designed for elderly PCNSL patients (with a median OS ranging from 14 to 17.5 months).^{7,10-12}

In summary, the Nordic PCNSL study was finalized as planned 10 years after the end of treatment. Seventeen of 66 patients were alive and in good health based on their PS (ECOG PS of 0-1 in most of the long-term survivors), MMSE, and FIM scores (at or close to the maximum level in almost all long-term survivors). We conclude that, in our study, consolidation with maintenance temozolomide has been beneficial regarding survival in vulnerable elderly PCNSL patients. Based on our results, we suggest future clinical trials for elderly PCNSL patients to study novel agents in combination with a HD-MTX-based induction immunochemotherapy regimen without HD-cytarabine, followed by maintenance temozolomide consolidation. Additional, preferably randomized, studies, are warranted to clarify whether consolidation with maintenance therapy could be of benefit to sustain remission and improve survival also in younger PCNSL patients, particularly those that are not fit for dose-intensive consolidation therapy. Having the potential for late relapses and neurotoxicity in mind, we find that all prospective PCNSL clinical trials should routinely report at least 10-year follow-up results in the future.

Authors

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Disclosures

No conflicts of interest to disclose.

Contributions

EJP was the principal investigator (PI) of the study, the national PI in Denmark, responsible for the design of the study, data management, accrual of patients in Denmark, and wrote the manuscript together with MP. MRS performed data analysis. OK was involved in protocol planning, was the national PI in Finland, and responsible for accrual of patients in Finland. UMF was involved in protocol planning, was the national PI in Norway, and responsible for accrual of patients in Norway. ME was involved in protocol planning, was the national PI in Sweden, and responsible for accrual of patients in Sweden. ØF, BØ, and AF recruited and treated patients in Norway. SL recruited and treated patients in Finland. ME recruited and treated patients in Sweden. TEG, HK, KP, ML, and MBP are current members of the Nordic Primary Central Nervous System Lymphoma Group and were involved in writing the manuscript. MP is the chair of the Nordic Primary Central Nervous System Lymphoma Group, the corresponding author of this study, performed data analysis together with MRS, and wrote, revised as well as reformatted the manuscript together with EJP.

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Data-sharing statement

No shared data are available.

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