

HDMTX-based polychemotherapy including intraventricular therapy in elderly patients with primary CNS lymphoma: a single center series

Sabine Seidel¹, Thomas Kowalski, Michelle Margold, Alexander Baraniskin, Roland Schroers, Peter Martus and Uwe Schlegel

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Abstract

Background: To investigate outcome and toxicity of high-dose systemic methotrexate (HDMTX)-based polychemotherapy and intracerebroventricular (ICV) chemotherapy via an Ommaya reservoir in elderly patients with primary central nervous system lymphoma (PCNSL).

Methods: We performed a retrospective analysis on patients ≥ 65 years with first diagnosis of PCNSL admitted to our center between January 2015 and December 2019. These patients were treated with a standardized chemotherapy protocol in case of absent contraindications for HDMTX-based chemotherapy. The protocol contained induction therapy with systemic rituximab, methotrexate and ifosfamide and consolidation treatment with systemic cytarabine (AraC) and ICV methotrexate, prednisolone and AraC.

Results: Of a total of 46 patients seen in this period, 3 did not qualify for HDMTX. Thus, 43 patients were included in this analysis. Median age was 74 years (range 65–86), median Karnofsky performance score was 50 (range 20–90). Of the 43 patients, 32 (74.4%) completed treatment including ICV therapy. Complete remission/complete remission unconfirmed was achieved in 26 of 43 patients (60.5%), partial response (PR) in 3 (7%); 5 (11.6%) had progressive disease, and 3 (7.0%) died due to treatment-related complications; in the remaining 6 (14.0%) therapy could not be completed. Median progression free survival was 16 months (95% confidence interval 8–24 months) and median overall survival had not been reached after a median follow up of 23 months (range 1–52 months); the 75th percentile survival time was 12 months. No Ommaya reservoir infection was observed. Complications of ICV treatment were pericatheter leucencephalopathy in two patients and surgical scar dehiscence with cerebrospinal fluid leak in one patient.

Conclusion: Toxicity of HDMTX plus ICV chemotherapy for elderly patients with PCNSL was manageable and outcome was excellent for patients treated with this protocol.

Keywords: PCNSL, intracerebroventricular chemotherapy, Ommaya reservoir, modified Bonn protocol

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Introduction

Primary central nervous system lymphomas (PCNSL) account for 1.9% of primary CNS tumors.¹ About half of the patients with PCNSL are older than 70 years.² While treatment options

and prognosis for younger patients with PCNSL have improved significantly over the last decades, the poor prognosis of elderly patients virtually remains unchanged.³ Whole brain radiation therapy (WBRT) may lead to severe neurocognitive

Correspondence to:
Sabine Seidel
Department of Neurology,
Knappschaftskranken
haus, University Hospital
Bochum, In der Schornau
23–25, Bochum, 44892,
Germany
sabine.seidel@kk-
bochum.de

Thomas Kowalski
Michelle Margold
Uwe Schlegel
Department of Neurology,
Knappschaftskranken
haus, University of
Bochum, Bochum,
Germany

Alexander Baraniskin
Roland Schroers
Department of Hematology
and Oncology, Knappsch
aftskrankenhaus,
University of Bochum,
Bochum, Germany

Peter Martus
Department of
Biostatistics and Clinical
Epidemiology, University
of Tübingen, Tübingen,
Germany



decline particularly in elderly patients,⁴⁻⁶ and is not included in the majority of currently used first-line protocols for elderly patients. The largest chemotherapy-only trials on elderly patients with PCNSL are the single arm PRIMAIN trial (patients ≥ 65 years),⁷ and a randomized phase-II trial conducted by the French ANOCEF-GOELAMS group (patients ≥ 60 years).⁸ In both trials, non-myeloablative high dose methotrexate (HDMTX)-based polychemotherapy regimens had been investigated, having achieved median overall survival (OS) times of 20.7 months [HDMTX, procarbazine, vincristine, cytarabine (AraC)],⁷ 14 months (MTX, temozolomide), and 31 months (HDMTX, procarbazine, vincristine, AraC).⁸ Median progression free survival (PFS) was 10.3,⁷ 6.1, and 9.5 months,⁸ respectively. High-dose chemotherapy with autologous stem cell transplantation (HD-ASCT), which is a first-line treatment used increasingly in younger patients, may be an option for carefully selected “biologically young” elderly patients with PCNSL,⁹ but the majority of elderly patients do not qualify for such intensive chemotherapy regimens.

Intracerebroventricular (ICV) chemotherapy is not part of the majority of currently used chemotherapy protocols for PCNSL; however, ICV increases cytostatic drug levels within the cerebrospinal fluid (CSF) compartment without adding systemic toxicity.¹⁰ In a trial on 65 patients treated with HDMTX-based polychemotherapy and ICV therapy *via* an Ommaya reservoir (Bonn protocol), 35 patients were >60 years of age at the time of diagnosis. For these patients, median OS was 34 months [95% confidence interval (CI) 21–40 months], but the results were hampered by a 19% rate of Ommaya reservoir infections in the entire cohort.^{11,12} Yet, a trial on the same protocol without ICV treatment for patients <60 years was stopped prematurely because of a high rate of early relapses, mainly leptomeningeal.¹³ Postponement of ICV treatment after induction therapy with three cycles of systemic rituximab, methotrexate, and ifosfamide resulted in a reduced reservoir infection rate of 9% in younger patients (<65 years) treated with a regimen based on the original Bonn protocol (modified Bonn protocol).¹⁴ Elderly patients (≥ 65 years) treated with the same modified Bonn protocol, but without ICV treatment, experienced a median PFS of 6.4 months (95% CI 2.1–10.7) and a median OS of 14.6 months (95% CI 5.4–23.9) only.¹⁴

At our center, these results led to a change in treatment strategy and ICV treatment was planned for all elderly patients from 2015 onwards, but was initiated after completion of three systemic induction cycles and if treatment response [complete remission (CR), complete remission unconfirmed (CRu) or partial remission (PR)] could be achieved by induction therapy. This study is a monocentric retrospective analysis on outcome and toxicity in a cohort of 43 patients ≥ 65 years with PCNSL treated with MTX-based polychemotherapy and ICV therapy (modified Bonn protocol).

Methods

All HIV-negative patients aged 65 years or older with first diagnosis of PCNSL, who presented at our center between January 2015 and December 2019, were identified. In January 2015, we defined the protocol as presented in Table 1 as standard in our clinic for all patients ≥ 65 years with PCNSL and without contraindications for HDMTX-based chemotherapy. Baseline staging included gadolinium-enhanced brain magnetic resonance imaging (MRI), slit-lamp examination, whole body fluorodeoxyglucose positron emission tomography (FDG PET) or computed tomography (CT) of neck, chest, and abdomen, bone marrow biopsy and lumbar puncture, if not contraindicated. All patients had an echocardiography to evaluate cardiac function (heart insufficiency NYHA grade III b and IV was an exclusion criteria for treatment with HDMTX).¹⁵ Renal scintigraphy was performed to determine the glomerular filtration rate (GFR), in order to disclose renal insufficiency as contraindication against HDMTX.

Rituximab was given at a dosage of 375 mg/m², systemic HDMTX was administered as a 4-h infusion under vigorous hydration and urine alkalization at a dosage of 4000 mg/m² if the GFR was ≥ 100 ml/min, at 3000 mg/m² (75%) for patients with a GFR of 75–99 ml/min, and at 2000 mg/m² (50%) for patients with a GFR of 50–74 ml/min. A GFR of <50 ml/min was considered a contraindication for treatment with HDMTX. Ifosfamide was administered at a dose of 800 mg/m² as a 1-h infusion with sodium 2-mercaptoethane sulfonate protection. AraC was given in a dose of 3000 mg/m² body-surface area as a 3-h infusion. All patients received prophylactic granulocyte colony-stimulating factor

Table 1. Chemotherapy protocol.

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Cycle 1–3 (1 cycle = 2 weeks)							
- Rituximab 375 mg/m ² i.v.	x						
- MTX 4000 mg/m ² i.v.		x					
- Ifosfamide 800 mg/m ² i.v.			x	x	x		
Cycle 4 + 6 (1 cycle = 3 weeks)							
- AraC 3000 mg/m ² i.v.		x	x				
- MTX 2.5 mg + prednisolone 3 mg ICV				x	x	x	
- AraC 10 mg intraventricular							x
Cycle 5 (1 cycle = 2 weeks)							
- MTX 4000 mg/m ² i.v.		x					
- Ifosfamide i.v. 800 mg/m ² i.v.			x	x	x		
- MTX 2,5 mg + prednisolone 3 mg ICV			x	x	x		
- AraC 10 mg intraventricular						x	
AraC, cytarabine; ICV, intracerebroventricular; i.v., intravenous; MTX, methotrexate.							

(G-CSF) as well as sulfamethoxazole + trimethoprim and aciclovir at each cycle.

Response was determined according to International PCNSL Collaborative Group (IPCG) criteria.¹⁶ Toxicity was classified according to the Common Toxicity Criteria (CTC, version 5.0). Patients were included in a follow-up program with clinical and MRI controls every 3 months for 2 years, every 6 months for the following 3 years, and then annually. Data were gained from patient charts in our clinic. Neither the patients themselves, nor the general practitioners were contacted. Retrospective analysis of this data was permitted by the local Ethics Committee (University of Bochum, Faculty of Medicine, approval number 20-6818-BR).

OS was calculated from the date of histologic diagnosis to death of any cause, or last date of follow up. PFS was defined as the time from date of histologic diagnosis to progression, death of any cause (if progression was not determined), or last date of follow up. OS and PFS were estimated by the Kaplan–Meier method. Log-rank tests were used to compare OS and PFS between groups. A

multivariate analysis was performed using the Cox proportional hazard regression model. The level of significance was 0.05 (two-sided). Analyses were conducted using SPSS version 23.0.

Results

Patient characteristics and treatment

A total of 46 patients 65 years or older with therapy-naïve PCNSL presented at our center between January 2015 and December 2019. Two patients were not eligible for MTX-based chemotherapy because of renal insufficiency and one refused treatment. In the following, data of the 43 patients who received HDMTX-based polychemotherapy and who were scheduled for ICV chemotherapy after induction is presented. Two patients (4.7%) were lost to follow up. Median follow up for surviving patients was 23 months (range 1–52 months). Median age was 74 years (range 65–86), median Karnofsky performance score (KPS) 50 (range 20–90); 13 patients (27.9%) had a KPS < 50. Of the 43 patients, 32 (74.4%) responded to induction therapy, proceeded to consolidation treatment including ICV

therapy, and completed treatment. For 38/43 patients (88.4%), dose reduction of MTX for adjustment to renal function was necessary [75% for 15 patients (34.9%), 50% for 23 patients (53.5%)]; 33 (76.7%) patients received dexamethasone at first diagnosis (the dose of dexamethasone was individualized as patients were referred from different hospitals). Patient characteristics are summarized in Table 2.

Treatment response, OS and PFS

Response to treatment was CR or CRu in 26 (60.5%) patients after completion of therapy. Three patients (7.0%) had PR. Two of these patients received HD-ASCT (one patient received HD-ASCT immediately after staging at completion of first-line treatment, one patient received HD-ASCT at progression), and one of these patients received a PI3K/mTOR-inhibitor within a clinical trial at progression. Five patients (11.6%) had progressive disease (PD) under induction therapy. In six patients (14.0%), therapy was terminated prematurely: one of these patients had a CR already after three cycles and treatment was stopped because of multiple infectious complications. Five patients had persistent poor clinical performance status (KPS ≤ 30) after two (three patients) or three (two patients) cycles of treatment, and received only symptomatic treatment then. Three patients (7.0%) died due to treatment related complications. One patient had cardiac arrest for unknown reasons, one had liver failure because of reactivation of asymptomatic hepatitis B undetected prior to treatment and one suffered from prolonged myelosuppression and died from septicemia. Of six patients with initial CSF involvement, four responded to treatment, of which three had CR on cerebral MRI and in the CSF and one showed PR on cerebral MRI, while CSF cytology after completion of treatment was negative. Two of those six patients did not receive ICV treatment, one for progression under therapy, and one, since treatment was terminated prematurely, due to infectious complications.

Median PFS was 16 months (95% CI 8–24 months, Figure 1). The 1-year PFS rate was 61%, 2-year PFS 40%, and 3-year PFS 16%. Median OS was not reached (75th percentile survival time 12 months; see Figure 2). The 1-year OS rate was 76%, the 2-year OS rate 66%, and the 3-year OS rate 50%.

Predictors of survival

The following factors were evaluated: age, KPS, sex, pre-treatment symptom duration >4 or ≤ 4 weeks, involvement of deep brain structures, elevation of lactate dehydrogenase (LDH) level in serum at first diagnosis, elevation of protein level in CSF at first diagnosis, first diagnosis in our center or at a different hospital and MTX dosage.

On univariate analysis we found a significant difference in this elderly cohort in OS but not in PFS for age groups <75 years ($n=22$) and ≥ 75 years ($n=21$). For patients <75 years median OS was not reached (75th percentile survival time 35 months) and for patients ≥ 75 years median OS was 15 months (95% CI 6–24 months, 75th percentile survival time 4 months, $p=0.002$, Figure 3). PFS was 19 months (95% CI 11–27 months) for patients <75 years and 8 months for patients ≥ 75 years (95% CI 0–19 months, $p=0.33$).

On multivariate analysis younger age and higher KPS were associated with longer OS, but not with longer PFS. For patients <75 years with a KPS >50 , for patients <75 years with a KPS ≤ 50 , and for patients ≥ 75 years with a KPS >50 , median OS was not reached (75th percentile survival time 35 months, 58 months and 8 months, respectively), for patients ≥ 75 years with a KPS ≤ 50 , median OS was 12 months (95% CI 0–26 months, 75th percentile survival time 2 months, Figure 4).

Toxicity

Hematologic and infectious complication were the most common toxic side effects. Details of grade 3 and 4 toxicity are summarized in Table 3.

Infectious complications were observed in 32 patients (74%); 18 patients had clinical signs of pneumonia or respiratory tract infection or radiological signs of pneumonia. No patient had to be intubated and in none bronchoscopy was performed. Thus, no pathogens had been isolated in tracheal secretion. One of these patients additionally harbored *Klebsiella pneumoniae* on the tip of the central venous access device. A total of 13 patients received piperacillin + tazobactam, 2 patients ampicillin + sulbactam, 2 patients ceftriaxone, and 1 patient meropenem. Urinary tract infection occurred in 11 patients. Isolated pathogens were *Escherichia coli* (four patients) and

Table 2. Patient characteristics (*n*=43).

	No. of patients
Age	
Median	74 years
Range	65–86 years
65–75	22 (51.2%)
≥75	21 (48.8%)
≥80	4 (9.3%)
Sex	
Male	23 (46.5%)
Female	20 (53.5%)
KPS	
Median	50
Range	20–90
<70	30 (69.8%)
<50	12 (27.9%)
<30	3 (7.0%)
Pre-treatment symptom duration	
Median	5 weeks
Range	3–20 weeks
>4 weeks	22 (51.2%)
≤4 weeks	21 (51.2%)
Histologic diagnosis	
DLBCL	42
B-cell lymphoma diagnosed from CSF	1
Involvement of deep brain structures	
Yes	21 (48.8%)
No	22 (51.2%)
CSF involvement	
Yes	6 (14%)
No	20 (46.5%)
Not done	17 (39.5%)

*(Continued)***Table 2.** (Continued)

	No. of patients
CSF protein	
>50 mg/dl	18 (41.9%)
<50 mg/dl	12 (27.9%)
Not done	13 (30.2%)
LDH in serum	
>224 U/l	19 (44.2%)
<224 U/l	24 (55.8%)
Number of chemotherapy cycles	
1 cycle	2 (4.7%)
2 cycles	3 (7.0%)
3 cycles	6 (14.0%)
4 cycles	0
5 cycles	0
6 cycles	32 (74.4%)
CSF, cerebrospinal fluid; DLBCL, diffuse large B-cell lymphoma; KPS, Karnofsky performance score; LDH, lactate dehydrogenase.	

Staphylococcus haemolyticus (one patient). Treatment was piperacillin + tazobactam (seven patients), ampicillin + sulbactam (two patients), ceftriaxone (one patient), and imipenem (one patient). In three patients, the source of infection was not found; these patients received piperacillin + tazobactam.

The following complications related to ICV treatment were observed: In three patients a misplacement of the Ommaya reservoir was seen on the routine CT scan after implantation, and placement had to be corrected. ICV chemotherapy was then continued without complications.

Three patients had symptomatic non-infectious complications associated to ICV treatment: one patient developed a surgical scar dehiscence with CSF leak several weeks after completion of therapy, and the reservoir was removed. Two patients had symptomatic pericatheter leucoencephalopathy without signs of increased intracranial pressure. In one of these patients, transient memory problems and agitation were observed during the 5th cycle of

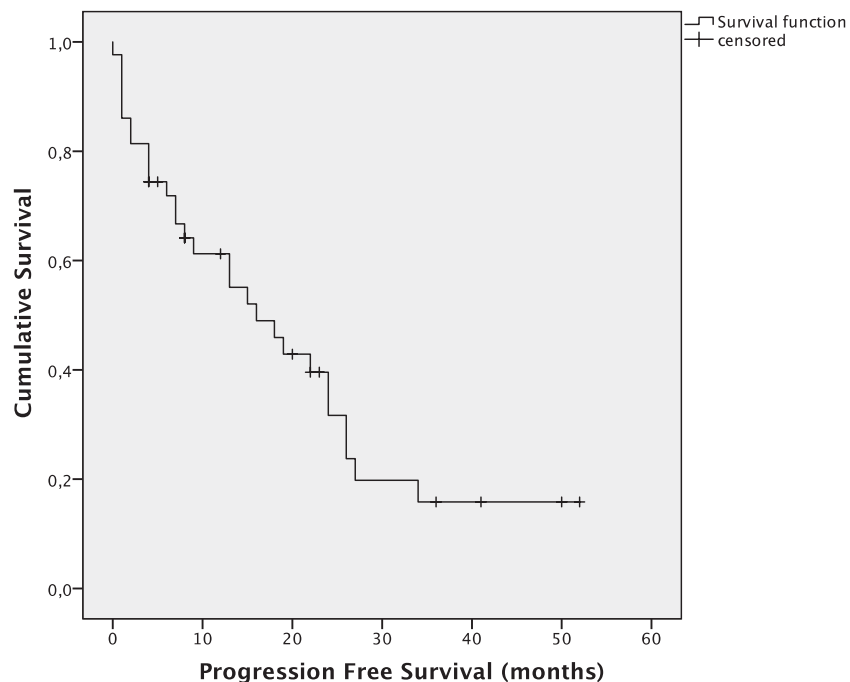


Figure 1. PFS ($n=43$).
PFS, progression free survival.

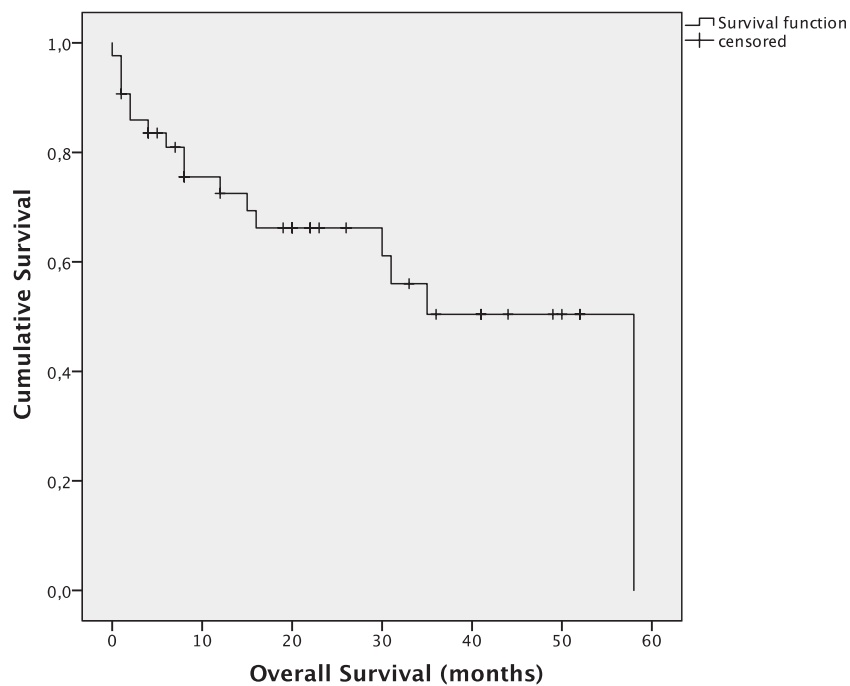


Figure 2. OS ($n=43$).
OS, overall survival.

therapy. This patient recovered completely from symptoms within 4 days, the reservoir was left in place and systemic chemotherapy was completed

without intraventricular therapy. The other patient, an 83-year-old patient with severe psychomotor slowing at first diagnosis (PCNSL

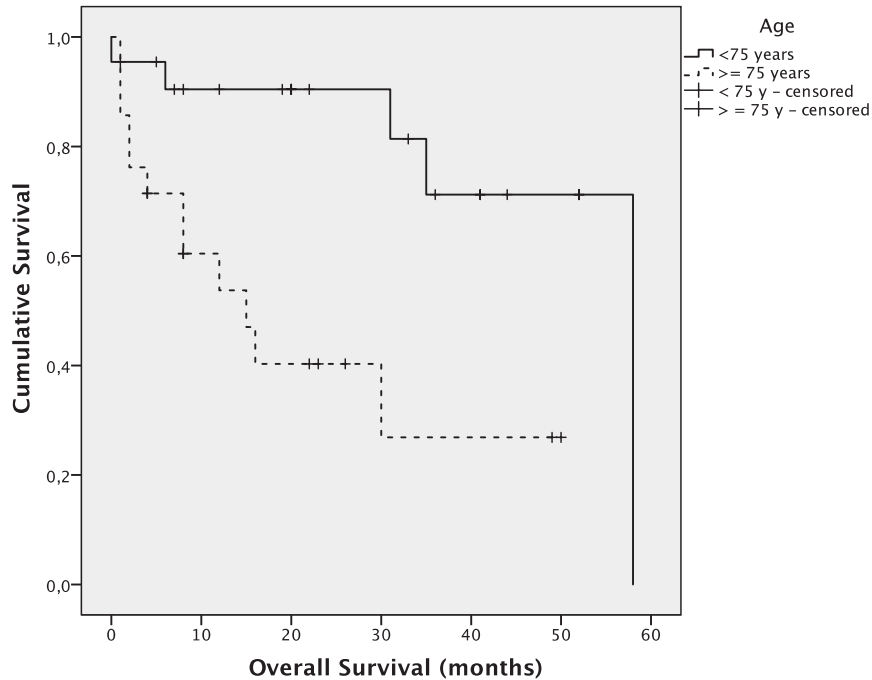


Figure 3. OS according to age ($n=43$).
OS, overall survival.

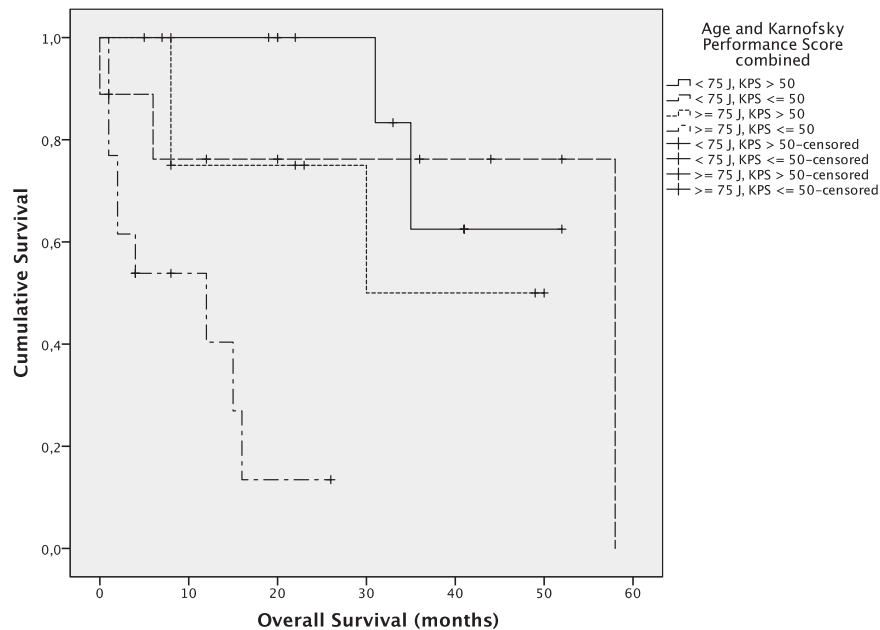


Figure 4. OS according to age and KPS ($n=43$).
KPS, Karnofsky performance score; OS, overall survival.

localization in the right frontal and parietal lobe and in the splenium) did not recover completely from neuropsychiatric symptoms, even though CRu was seen on MRI after completion of

therapy. On MRI after completion of therapy, T2-hyperintensities around the catheter were detected, which had not been visible on a CT scan after the 4th cycle of chemotherapy.

Table 3. CTC grade 3–4 toxicity ($n=43$).

	Grade 3	Grade 4
Hematologic		
Anemia	18 (42%)	7 (16%)
Leucopenia	13 (30%)	8 (19%)
Neutropenia	10 (23%)	20 (47%)
Lymphopenia	3 (7%)	37 (86%)
Thrombocytopenia	9 (21%)	16 (37%)
Non-hematologic		
Infection	32 (74%)	–
Thrombosis	8 (19%) ^a	2 (5%)
Increase of transaminases	18 (42%)	1 (2%)
Retroperitoneal bleeding	–	1 (2%)
Mucositis	–	1 (2%)
Nausea	1 (2%)	–
Tachyarrhythmia	1 (2%)	–
Low serum potassium	–	1 (2%)

^aSeven of eight patients suffered from jugular vein thrombosis as a consequence of central venous access devices, one had deep vein thrombosis, despite antithrombotic prophylaxis. CTC, common terminology criteria.

A deterioration of neurocognitive symptoms, including somnolence and agitation during the 5th and 6th cycle had been observed, but the patient suffered concomitantly from pneumonia during the 5th cycle. After recovery from pneumonia, psychomotor slowing improved to the status before the infection. After completion of treatment and rehabilitation, the patient was able to live at home and to manage activities of daily living independently with some support from their family and a nursing service. No reservoir infection and no hemorrhage associated with the implantation of the Ommaya reservoir were observed.

Salvage treatment

Five patients progressed under therapy and 13 relapses were observed after a range of 7–34 months. All first relapses were cerebral; no systemic nor ocular relapse was observed. All relapses were located in the brain parenchyma.

CSF cytology at relapse was available in three patients only, all of which had negative results. No isolated leptomeningeal relapse was observed. However, lumbar puncture at routine follow up and at relapse was performed only in case of clinical suspicion of leptomeningeal relapse.

A second-line therapy was applied to 17 patients. Seven patients (median age 67 years, range 66–72 years) were treated with HD-ASCT at progression or relapse. Two patients received WBRT. Five patients received rituximab, HDMTX (MTX-re-challenge) and temozolomide, and three patients received rituximab and temozolomide. One patient decided against further tumor-specific treatment and received symptomatic treatment alone. At second relapse ($n=5$) two patients received WBRT, one received rituximab and temozolomide, one patient received intraocular rituximab for ocular relapse, and one received palliative treatment only.

Discussion

The aim of this retrospective study was to evaluate the feasibility, efficacy and safety of HDMTX-based polychemotherapy including ICV treatment in elderly patients (≥ 65 years) with PCNSL.

Since late neurotoxicity as a consequence of WBRT especially affects elderly patients,^{4–6} many trials in the last 20 years have focused on chemotherapy only treatment strategies in this population. Most recent trials draw the line between younger and elderly PCNSL patients at 65 years,^{7,17–19} as was the case in our study, whereas other trials defined “elderly” as patients >60 years of age.^{4,8,11,20–24} The trial results on patients with a lower age limit of 60 years were nevertheless considered for interpretation of our results.

Chemotherapy only trials in elderly patients report median OS of 14.3–49.2 months and median PFS of 5.9–19.5 months (for details see Table 4).^{4,7,8,11,14,17–24} Results with the regimen applied in this retrospective study compare favorably with results of other chemotherapy only regimens, regarding the poor clinical condition of this unselected group of consecutive elderly patients referred to this center with a median KPS of 50, and with 13/43 patients with a KPS <50 at first diagnosis. The vast majority of patients referred to our center was able to receive the planned chemotherapy protocol: Of 46 patients, 43 patients received HDMTX-based chemotherapy, and 32 patients completed treatment including ICV therapy.

We observed a significantly longer median OS for patients aged 65–74 years as compared with patients ≥ 75 years [OS not reached *versus* OS 15 months (95% CI 6–24 months)]. The difference in survival according to age in our cohort is probably not only due to the age difference itself, but also due in part to better therapeutic options at relapse for “younger” patients. In our series, nine patients received HD-ASCT at progression under therapy ($n=3$), relapse ($n=4$), or PR only ($n=2$) after first-line treatment (age range 66–72 years). In other trials on elderly patients with PCNSL, HD-ASCT was applied in 2/15 patients and 2/63 with disease progression or relapse.^{8,22} One study explicitly included patients not able to receive HD-ASCT.¹⁷ As there is increasing evidence of efficacy and tolerability of HD-ASCT

for selected “biologically young” elderly patients,⁹ it might be considered more often first line for those in the future. Yet, considering that about half of patients with PCNSL are older than 70 years,² the need for effective treatment strategies for patients not able to receive HD-ASCT is of major importance.

The inclusion of ICV treatment is a distinctive feature of this study, as ICV treatment is not part of most chemotherapy protocols for PCNSL. Apart from the trial on the original Bonn protocol,^{11,12} on which the present regimen is based, only one other trial with inclusion of elderly patients applied ICV treatment *via* an Ommaya reservoir.⁴ In this latter trial, a reservoir infection rate of 2% (one of 52 patients without details on the age of this patient) was reported. While the Bonn protocol reported a 19% reservoir infection rate,¹¹ a modified Bonn protocol with postponement of ICV treatment to a timepoint after three systemic induction cycles was associated with a 9% reservoir infection rate in patients <65 years.¹⁴ In the present study, we did not observe reservoir infections at all, despite the application of ICV treatment to an elderly and frail patient population. For application of ICV chemotherapy, strict antiseptic rules had been implemented at our hospital.²⁵ While no infectious complications occurred, non-infectious complications were observed in three patients (two patients with pericatheter leucencephalopathy, one patient with surgical scar dehiscence and CSF leak); however, these complications were manageable and long-term sequelae could be avoided.

Grade 3 and 4 hematological and infections were more common in our series compared with other studies on elderly patients^{7,8,17,21}; yet, only one patient suffered from sepsis and died (Table 3). Three patients (7.0%) died from treatment-related complications, which is comparable with the 2–10% reported in other studies.^{7,8,17,18,21,22}

This study has several limitations. First, even though the chemotherapy protocol was standardized, it is a retrospective study. Second, a potential selection bias of patients treated cannot be ruled out, since elderly patients in a very poor clinical condition seen in other hospitals might not have been referred to this tertiary care center. Third, the sample size is relatively small and median follow up is rather short.

Table 4. HDMTX-based polychemotherapy regimens without whole brain radiotherapy in first-line treatment for elderly PCNSL patients (trials including >20 patients).

Author	Regimen	n	Design	Age limit	CR/CR u-rate	Median PFS	Median OS	Median age/KPS
Abrey <i>et al.</i> ^{4a}	MTX, procarbazine, vincristine, ICV MTX	22	pros single	>60 years	n.r.	n.r.	33 m	n.r.
Pels <i>et al.</i> ¹¹ ; Juergens <i>et al.</i> ^{12a}	MTX, vincristine, ifosfamide, cyclophosphamide, vindesine, AraC, dexamethasone, ICV MTX/AraC/prednisolone	35	pros single	>60 years	47%	7 m (TTF)	34 m	n.r.
Hoang-Xuan <i>et al.</i> ²¹	MTX, CCNU, procarbazine, methylprednisolone, IT MTX/AraC	50	pros single	>60 years	42%	6.8 m	14.3 m	72 years/50
Omuro <i>et al.</i> ²²	MTX, TMZ	23	retro single	>60 years	55%	8 m (EFS)	35 m	68 years/60
Illerhaus <i>et al.</i> ¹⁷	MTX, procarbazine, CCNU	30	pros single	>65 years ^b	44.4%	5.9 m	15.4 m	70 years/60
Olivier <i>et al.</i> ²³	MTX, vindesine, prednisolone, idarubicine	35	pros single	60–70 years	17%	13 m	19 m	65 years/70
Fritsch <i>et al.</i> ¹⁸	rituximab, MTX, procarbazine, CCNU	28	pros single	≥65 years	64%	16 m	17.5 m	75 years/60
Omuro <i>et al.</i> ⁸	1: MTX, TMZ 2: MTX, procarbazine, vincristine, AraC	98	pros rand	≥60 years	1: 45% 2: 62%	1: 6.1 m 2: 9.5 m	1: 14 m 2: 31 m	72 years/70
Pulczynski <i>et al.</i> ¹⁹	rituximab, MTX, AraC, ifosfamide, cyclophosphamide, TMZ, IT liposomal AraC	27	pros single	66–75 years	57.7%	n.r.	not reached	70 years/ n.r.
Fritsch <i>et al.</i> ⁷	rituximab, MTX, procarbazine, CCNU	107	pros single	≥65 years	35.5%	10.3 m	20.7 m	73 years/70
Houillier <i>et al.</i> ²⁰	rituximab, MTX, procarbazine, vincristine, intensified cytarabine	90	retro single	≥60 years	55%	10 m	28.1 m	68 years/60
Seidel <i>et al.</i> ¹⁴	rituximab, MTX, ifosfamide, AraC ^c		retro single	≥65 years	n.r.	6.4 m	14.6 m	n.r.
Bromberg <i>et al.</i> ²⁴	1: MTX, BCNU, teniposide, prednisone 2: rituximab, MTX, BCNU, teniposide, prednisone	105	pros rand	61–70 years	n.r.	1:19.5 m 2:14.6 m	1:49.2 m 2:34.9 m	n.r.
Our study	rituximab, MTX, ifosfamide, AraC, ICV MTX/AraC/prednisolone	43	retro single	≥65 years	60.5%	16 m	not reached	74 years/50

^aTrial included also younger patients, but reported the outcome of elderly patients separately.

^bn = 3 <65 years but not able to receive HD-ASCT.

^cn = 8 received ICV treatment with MTX/AraC/prednisolone as they were considered biologically younger.

AraC, cytarabine; BBBB, blood brain barrier disruption; BCNU, carmustine; CCNU, lomustine; HD-ASCT, high-dose chemotherapy with autologous stem cell transplantation; HDMTX, high-dose systemic methotrexate; ICV, intracerebroventricular; ifo, ifosfamide; IT intrathecal; MTX, methotrexate; n.r., not reported; OS, overall survival; PFS, progression free survival; pros, prospective; rand, randomized; retro, retrospective; single, single arm; TMZ, temozolomide; TTF, time to treatment failure.

Nevertheless, the results of this study are promising, and, in our view, encourage investigation of the additional value of ICV treatment in elderly patients as an appropriate modality to intensify therapy in a prospective randomized trial.

Conflict of interest statement

S. Seidel declares that there is no conflict of interest.

T. Kowalski declares that there is no conflict of interest.

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A. Baraniskin declares that there is no conflict of interest.

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ORCID iD

Sabine Seidel  <https://orcid.org/0000-0002-1671-3297>

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