Twenty-year follow-up of a pilot/phase II trial on the Bonn protocol for primary CNS lymphoma

Sabine Seidel, MD, Hendrik Pels, MD, Sabine Schlömer, PhD, Annika Kowoll, MD, Klaus Fliessbach, MD, PhD, Andreas Engert, MD, Marlies Vogt-Scheden, MD, Gerlinde Egerer, MD, Heinz Reichmann, MD, PhD, Gabriele Schackert, MD, Frank Kroschinsky, MD, Martina Deckert, MD, Ulrich Herrlinger, MD, Thomas Kockgether, MD, PhD, Rolf Fimmers, PhD, Udo Bode, MD, Ingo G.H. Schmidt-Wolf, MD, and Uwe Schlegel, MD

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Abstract

Objective
To determine whether a fraction of patients with primary CNS lymphoma (PCNSL) had been cured by systemic and intraventricular methotrexate- and cytarabine-based chemotherapy (Bonn protocol) after a very long-term follow-up of nearly 20 years.

Methods
Sixty-five patients (median age 62 years, range 27–75; median Karnofsky performance score 70, range 20–90) had been treated with systemic and intraventricular polychemotherapy without whole brain radiotherapy from September 1995 until December 2001. All patients still alive in 2019 were contacted and interviewed on their current life situation.

Results
Median follow-up for surviving patients was 19.6 years (17.5–23.3 years). Out of 65 patients, 11 (17%) were still alive. Six of those never experienced any relapse. For the whole study population, median overall survival (OS) was 4.4 years (95% confidence interval [CI] 2.9–5.9); for patients ≤60 years, 11.0 years (95% CI 4.8–17.0). The 10-year OS rate for the entire cohort was 29% and the estimated 20-year OS rate was 19%. Four late relapses were observed after 9.8, 10.3, 13.3, and 21.0 years.

Conclusion
At a median follow-up of 19.6 years, 17% of patients were alive and free of tumor; however, even after response for decades, an inherent risk of relapse, either systemic or cerebral, characterizes the biology of PCNSL.

Classification of evidence
This work provides Class III evidence that PCNSL treatment with methotrexate-based polychemotherapy including intraventricular therapy is associated with long-term disease control in some patients.
Primary CNS lymphomas (PCNSLs) are highly aggressive diffuse large B-cell lymphomas with a worse prognosis than their systemic counterparts. In the past 2 decades, treatment developments in PCNSL focused on establishing effective radiation-free or reduced dose radiation protocols to avoid late cognitive decline after whole brain radiotherapy. For most of these trials, no long-term data are available. There is one study with a follow-up period of up to 23 years on 149 patients with PCNSL treated with intraventricular methotrexate after osmotic blood–brain barrier disruption (BBBD) that reported a median overall survival (OS) of 3.1 years, a 5-year OS rate of 41%, and an 8.5-year OS rate of 25%.

The Bonn protocol was one of the first radiation-free protocols. It produced promising results that had been reported on in 2003 and 2010. In a multicenter pilot/phase II trial, 65 patients had been treated with high-dose methotrexate- and cytarabine-based systemic therapy in combination with intraventricular methotrexate, prednisolone, and Ara-C. Durable responses in a high fraction of patients were observed (median OS 54 months) without neurocognitive decline at long-term follow-up. For patients ≤60 years, median OS had not yet been reached after a median follow-up of 100 months with a survival rate at 100 months of 57%. According to these results, we concluded that the Bonn protocol might be curative for PCNSL in a fraction of patients, particularly in younger patients. We carried out this very long-term follow-up to further substantiate this assumption.

The trial was conducted from 1995 to 2001 and had therefore not been registered by ClinicalTrials.gov.

### Statistical analysis
OS was calculated from the date of histologic diagnosis to death or last date of follow-up. Time to treatment failure (TTF) was defined as time from onset of treatment to disease progression or relapse, death from any cause, discontinuation of treatment because of any cause, or last date of follow-up. OS and TTF were estimated by the Kaplan-Meier method. Log-rank tests were used to compare survival between patient groups. The significance level was set at \( p < 0.05 \). A competing risk of death analysis was done comparing disease-related death and death for other reasons.

### Standards protocol approvals, registration, and patient consent
The ethics committees of the Faculties of Medicine of the Universities involved in treatment had approved the study. Written informed consent was obtained from all participants. The trial was conducted from 1995 to 2001 and had therefore been registered by ClinicalTrials.gov.

### Data availability
Anonymized data can be shared by request from any qualified investigator.

### Classification of evidence
This work provides Class III evidence that treatment of PCNSL with methotrexate-based polychemotherapy including intraventricular therapy is efficient and is associated with long-term disease control in a fraction of patients (after a median follow-up of 19.6 years, 17% of patients were alive).

### Results

#### Patient characteristics
In March 2019, a total of 65 patients was evaluated. Median age of all patients was 62 years (range 27–75 years) at first diagnosis, 30 of 65 patients were 60 years or younger, and 34 patients were male. Median Karnofsky Performance Scale score (KPS) was 70 (range 20–90). Sixteen patients (25%) had a KPS of ≤50 at first diagnosis. One of 65 patients had ocular involvement at first diagnosis. Intraventricular therapy was applied in 64 patients; 1 patient refused intraventricular treatment. Median follow-up for surviving patients was 19.6 years.
years (range 17.5–23.3 years). One patient was lost to follow-up 21 years after first diagnosis (while reportedly alive and free of relapse). For 8 patients (12%), the cause of death was unknown.

**Survival analysis**

Median OS for all patients was 53 months (95% confidence interval [CI] 35–71 months), 5-year OS 43%, 10-year OS 29%, and the Kaplan-Meier survival estimate at 20 years 19%. Median OS for patients ≤60 years was 11 years (132 months, 95% CI 57–204 months), and for patients >60 years, 33 months (95% CI 19–47 months, p < 0.001; figure). For patients ≤60 years, the 5-year OS was 70%, 10-year OS 53%, and the estimated 20-year OS 39%. For patients >60 years 5-year OS was 23%, 10-year OS 9%, and the estimated 20-year OS 3%. Median TTF was 21 months (95% CI 6–36 months) for all patients. Median TTF for patients ≤60 years was 41 months (95% CI 7–75 months), and for patients >60 years, 5 months (95% CI 0–18 months, p < 0.001).

**Initial response, response duration, and long-term survival**

Of the entire cohort of 65 patients, 37 showed CR, 6 partial response (PR), 12 progressive disease, and 6 early death (ED) (table 1). Four responses were not assessable after complete resection of tumor (2 patients) or treatment termination after 1 cycle according to the patient’s (1 patient) or the participating center’s (1 patient) decision. One patient with PR was irradiated after incomplete chemotherapy as a result of nephrotoxicity, 1 patient with PR discontinued chemotherapy and received no further treatment, and the other 4 patients with PR showed only minimal residual lymphoma on MRI after completion of treatment and no further therapy was applied (complete response unconfirmed according to current criteria).

Excluding patients with progressive disease and ED, in the remaining 47, a total of 36 documented first relapses occurred during follow-up (25 cerebral, 5 systemic, 1 systemic and cerebral, 5 ocular) after 5 months up to 251 months.

At follow-up in March 2019, 11 of 65 patients (17%) were still alive. Six of those never experienced a relapse. Five of 11 long-term survivors experienced first relapse (3 systemic, 1 cerebral, 1 ocular) after 7 up to 117 months and 3 patients also had second relapse (1 ocular, 2 cerebral) (table 2). Ten of 11 surviving patients were living at home at follow-up. One patient lived in a care facility after having had major cerebral ischemia. Three patients were still working. Five patients were retired but living independently at home (current age 72–80 years); 1 of these patients was the caregiver of his wife. For 2 patients, the current working status is unknown.

All long-term survivors were 60 years or younger at first diagnosis (range 28–60 years). Seven of 11 patients were female. Eight of 11 patients had a KPS of ≤70 and 1 of 11 had a KPS of ≤50 at first diagnosis. For 9 patients, the initial lactate dehydrogenase (LDH) serum value was available and 1 had elevated LDH at first diagnosis. For 9 patients, CSF sample data were available. Four of 9 patients had elevated protein (>50 mg/dL) in CSF and 2 of 9 patients had lymphoma cells in CSF cytology. In 7 of 11 patients, deep brain structures were involved by the tumor. None of the 11 patients had ocular involvement at first diagnosis. For details on patient characteristics of long-term survivors, see also table 3.

Late relapses were observed in 4 patients after 9.8 (cerebral), 10.3 (systemic and cerebral), 13.3 (cerebral), and 21.0 (systemic) years (1 of these cases had already been published before). Both patients with isolated cerebral relapses were treated with the Bonn protocol a second time, which again induced CR. The patient with systemic and cerebral relapse was treated with high-dose chemotherapy with autologous stem cell transplantation (HD-ASCT) and died from treatment-related complications (sepsis). The patient with systemic relapse after 21.0 years was treated in another hospital unaware of the PCNSL diagnosis 21 years before. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) was applied and the patient died from treatment-related complications (severe pneumonia).

**Discussion**

This analysis represents a very long-term follow-up of 65 patients with PCNSL, who had been treated within a pilot/phase II trial between 1995 and 2001. Results of the trial were published in 2003 and in 2010 with long-term disease control in about half of the younger patients (60 years and younger) after a median follow-up of 100 months. This very
Table 1 Whole study cohort (n = 65): initial response to treatment and characteristics of relapse

| Response | N (%) | First relapse (interval to relapse, mo) | Treatment at first relapse |
|----------|-------|----------------------------------------|---------------------------|
| **CR**  | 37 (56.9) | 19 Cerebral** (9–230) | 6 Bonn protocol |
|          |        |                                        | 5 WBRT                   |
|          |        |                                        | 3 HD-ASCT                |
|          |        |                                        | 2 PCV                    |
|          |        |                                        | 1 Temozolomide           |
|          |        |                                        | 2 Unknown                |
|          |        | 4 Systemic (20–251)                    | 3 HD-ASCT                |
|          |        |                                        | 1 R-CHOP                 |
|          |        | 5 Ocular (5–58)                        | 5 Ocular RT              |
|          |        | 6 No relapse; alive                    |                          |
|          |        | 2 No relapse; death not from PCNSL     |                          |
|          |        | 1 Lost to follow-up**                  |                          |
| **PR**  | 6 (9.2) | 6 Cerebral (5–41)                      | 2 WBRT                   |
|          |        |                                        | 1 Bonn protocol          |
|          |        |                                        | 2 No further treatment   |
|          |        |                                        | 1 Unknown                |
| **Not assessable** | 4 (6.2) | 1 Cerebral (89)** | 1 WBRT |
|          |        | 1 Systemic (102)**                     | 1 HD-ASCT                |
|          |        | 2 CTX discontinuation**                |                          |
| **PD**  | 12 (18.5) | —                                      | 8 WBRT                   |
|          |        |                                        | 1 PCV                    |
|          |        |                                        | 2 No further treatment   |
|          |        |                                        | 1 Unknown                |
| **ED**  | 6 (9.2) | —                                      |                          |
|          | 65 (100) |                                        |                          |

Abbreviations: CR = complete remission; CTX = chemotherapy; ED = early death; HD-ASCT = high-dose chemotherapy with autologous stem cell transplantation; PCV = procarbazine, lomustine, vincristine; PD = progressive disease; PR = partial remission; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; WBRT = whole brain radiotherapy.

* Of 28 patients with a first relapse, 14 had second relapse (11 cerebral, 1 systemic, 2 ocular), 7 third relapse (4 cerebral, 3 ocular), 1 fourth relapse (cerebral); all relapses were treated on an individualized basis and treatment was documented to the best of our knowledge; not all relapses/salvage therapies were completely documented.

b Two patients who were treated with systemic chemotherapy had combined cerebral and ocular relapse; 1 patient had cerebral and systemic relapse and was treated with HD-ASCT.

c Lost to follow-up 20 year after first diagnosis while reportedly alive and disease-free.

Of 6 patients with a first relapse, 1 patient had second relapse (cerebral).

Of 2 patients with a first relapse, 2 had second relapse (cerebral).

f Complete resection of tumor prior to chemotherapy.

g This patient experienced an early relapse 7 months after first diagnosis due to incomplete first-line treatment (reservoir infection), received 6 complete cycles of the Bonn protocol, and had CR after complete therapy.

h Termination of treatment after 1 cycle according to the patient’s (1 patient) or the participating center’s (1 patient) decision.

long-term follow-up after a median of 19.6 years for surviving patients shows that even after decades of complete response, relapses may occur. The possibility to compare our long-term data to those of other trials on chemotherapy alone, on chemotherapy with reduced dose radiation, or on HD-ASCT is limited, since these studies report on a median follow-up of 2.8–5.9 years. In our study, we observed very long-term survival in 12 patients (11 with documented follow-up and 1 lost to follow-up after 21 years when she was reportedly alive and disease free). Of the 11 patients with documented follow-up, 3 patients were still working, 5 patients were retired but living independently, 1 patient lived in...
a nursing facility after stroke, and for 2 patients the working status is unknown. No formal neuropsychological testing was done in this study for logistic reasons as patients were currently living in different places all over Germany. The 11 long-term survivors with documented follow-up were all 60 years or younger at first diagnosis; only the patient lost to follow-up with survival of more than 20 years was older than 60 years at diagnosis. Disregarding this single elderly patient, 6 of 11 long-term survivors never experienced relapse after a minimum of 18.2 years since first diagnosis. It is tempting to speculate that these 6 long-term survivors had actually been cured of PCNSL. However, we observed 4 late relapses after up to 21 years. This observation does not allow us to conclude that PCNSL can be considered cured after a definite time frame. Our results are in analogy to the results of a study on intraarterial methotrexate after osmotic BBBD in 149 patients, which also resulted in a small fraction of patients with long-term disease control with a follow-up period of up to 23 years (1982–2005, no range of follow-up was given). A median OS of 3.1 years was observed for all patients in this study; 5.2 years for patients <60 years of age and 2.2 years for patients ≥60 years. The 5-year OS rate was 41% and 8.5-year survival rate 25% for all patients. Patients <60 years had a 5-year OS rate of 52% and reportedly there was a plateau in the survival curve after 8.5 years. Relapses were observed also in this study after up to 9.7 years.7 These similar outcomes of 2 patient populations treated with different methotrexate-based protocols resulting in similar long-term results supports the hypothesis of an inherent risk of relapse in PCNSL due to the biology of the tumor itself rather than by the protocol applied. The question whether treatment protocols including HD-ASCT will lead to improved very long-term survival and to less risk of late relapse can only be answered when 20-year follow-up data on those trials3,5,6 will be available.

We cannot answer whether in late relapses the same B-cell clone is present as at first diagnosis, since none of our patients underwent biopsy at relapse. In a retrospective analysis on 378 patients with heterogenous first-line treatment, 10 patients relapsed after more than 5 years, with a median time to first relapse of 7.4 years (range 5.2–14.6). For 1 patient in this retrospective series, the persistence of the original PCNSL clone was histologically confirmed at cerebral relapse; for the other 2 patients for whom tissue was available, the investigation was uninformative.18 Other studies suggested that lymphoma cells in PCNSL at first diagnosis and at systemic or cerebral relapses have common precursor cells but also harbor unique somatic mutations.19,20

### Table 2 Course of disease of long-term survivors

| Patient | Age, y/sex | First-line response | Relapse, y | Location | Salvage treatment | Response | Relapse 2, y | Location 2 | Salvage treatment 2 | Response | OS, y |
|---------|-------------|---------------------|------------|----------|------------------|----------|-------------|------------|------------------|----------|------|
| 1       | 28/F        | CR                  | No         | —        | —                | No       | —           | —          | —                | —        | >23.3|
| 2       | 51/M        | CR                  | No         | —        | —                | No       | —           | —          | —                | —        | >21.3|
| 3       | 60/F        | CR                  | No         | —        | —                | No       | —           | —          | —                | —        | >20.1|
| 4       | 55/M        | CR                  | No         | —        | —                | No       | —           | —          | —                | —        | >19.4|
| 5       | 51/M        | CR                  | No         | —        | —                | No       | —           | —          | —                | —        | >18.2|
| 6       | 33/M        | CR                  | No         | —        | —                | No       | —           | —          | —                | —        | >18.4|
| 7       | 52/F        | CR                  | 2.4        | Systemic | HD-ASCT (BEAM)   | CR       | No          | —          | —                | —        | >19.6|
| 8       | 40/F        | CR                  | 3.3        | Systemic | R-CHOEP+ HD-ASCT (BEAM) | CR | No | — | — | — | >17.5 |
| 9       | 60/F        | CR                  | 0.6        | Ocular   | Ocular RT        | CR       | 1.3         | Ocular     | Ocular RT        | CR       | >19.7|
| 10      | 55/F        | CR                  | 9.8        | Cerebral | Bonn protocol    | CR       | 12          | Cerebral   | HD-ASCT (BCNU/TT) | CR       | >17.6|
| 11      | 37/F<sup>a</sup> | NA<sup>b</sup>    | 8.5        | Systemic | R-CHOP + HD-ASCT (BEAM) + RT sacral bone | CR | 11 | Cerebral | HD-ASCT (BCNU/TT) | CR       | >20.8|

Abbreviations: BCNU = carmustine; BEAM = carmustine, etoposide, cytarabine, melphalan; CR = complete response; FD = first diagnosis; HD-ASCT = high-dose chemotherapy with autologous stem cell transplantation; NA = not assessable; OS = overall survival; R-CHOEP = rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, etoposide, prednisone; R-CHOEP+ = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RT = radiotherapy; TT = thiotepa.

<sup>a</sup>This patient experienced an early relapse 7 months after first diagnosis due to incomplete first-line treatment (reservoir infection), received 6 complete cycles of the Bonn protocol, and had CR after complete therapy.

<sup>b</sup>Complete resection of tumor prior to chemotherapy.
While durable responses with the Bonn protocol had been achieved with an estimated 20-year survival rate of 19%, the protocol had been criticized because of an Ommaya reservoir infection rate of 19%. We continue to use a modified version of the Bonn protocol at our clinic and by postponement of intraventricular therapy until the beginning of the fourth treatment cycle at the start of consolidation reduced Ommaya reservoir infection rates of 9% were achieved.

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**Disclosure**

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**Appendix Authors**

| Name                  | Location                          | Contribution                                      |
|-----------------------|-----------------------------------|--------------------------------------------------|
| Sabine Seidel, MD     | Knappschaftskrankenhaus University of Bochum | Designed and conceptualized study, analyzed and interpreted the data, wrote the manuscript |
| Hendrik Pels, MD      | Hospital Barmherzige Brüder, Regensburg | Major role in the acquisition of data, revised the manuscript for intellectual content |
| Sabine Schlömer, PhD  | Knappschaftskrankenhaus University of Bochum | Interpreted the data, revised the manuscript for intellectual content |
| Annika Kowoll, MD     | Knappschaftskrankenhaus University of Bochum | Major role in the acquisition of data, revised the manuscript for intellectual content |
| Klaus Fliessbach, MD  | University of Bonn                 | Major role in the acquisition of data             |
| Andreas Engert, MD    | University of Cologne              | Major role in the acquisition of data             |
| Marlies Vogt-Schaden, MD | University of Heidelberg           | Major role in the acquisition of data             |
| Gerlinde Egerer, MD   | University of Heidelberg           | Major role in the acquisition of data             |
| Heinz Reichmann, MD, PhD | University of Dresden               | Revised the manuscript for intellectual content |
| Gabriele Schackert, MD | University of Dresden               | Major role in the acquisition of data             |
| Frank Kroschinsky, MD | University of Dresden              | Major role in the acquisition of data             |
| Martina Deckert, MD   | University of Cologne              | Revised the manuscript for intellectual content |

Abbreviation: KPS = Karnofsky Performance Scale score.

**Table 3 Characteristics of long-term survivors (n = 11)**

| No. of patients | Age, y | KPS | involvement of deep brain structures | Lactate dehydrogenase elevation | CSF protein >50 mg/dL | Neuropathologic diagnosis | CSF involvement | Ocular involvement |
|-----------------|--------|-----|-------------------------------------|---------------------------------|-----------------------|-------------------------|------------------|-------------------|
|                 | ≤60    | >70 | Yes                                 | Yes                             | Yes                   | Highly malignant B-cell non-Hodgkin lymphoma | Yes              | Yes               |
|                 | >60    | ≤70 | No                                  | No                              | No                    | Other                   | No               | No                |
|                 |        |     | Not done                            | Not done                        | Not done              |                         |                  |                   |
|                 |        |     |                                      |                                 |                       |                         |                  |                   |
|                 |        |     |                                      |                                 |                       |                         |                  |                   |

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