Aus der Klinik für Hämatologie und Onkologie

der Medizinischen Fakultät

der Otto-von-Guericke-Universität Magdeburg

(Direktor: Prof. Dr. med. Thomas Fischer)

Comparison of the clinical outcome in primary CNS lymphoma patients treated inside and outside of a clinical trial

(Vergleich der klinischen Ergebnisse von Patienten mit primärem ZNS-Lymphom, die innerhalb und außerhalb einer klinischen Studie behandelt wurden)

Dissertation

zur Erlangung des Doktorgrades

Dr. med.

(doctor medicinae)

an der Medizinischen Fakultät

der Otto-von-Guericke-Universität Magdeburg

vorgelegt von Vanja Zeremski

aus Novi Sad, Serbien

Magdeburg 2017

Dokumentationsblatt

Bibliographische Beschreibung:

Zeremski, Vanja:

Vergleich der klinischen Ergebnisse von Patienten mit primärem ZNS-Lymphom, die innerhalb und außerhalb einer klinischen Studie behandelt wurden. - 2017, - 71 Bl., 12 Abb., 5 Tab., 2 Anl.

Kurzreferat

Primäre ZNS-Lymphome (PCNSL) sind seltene Lymphome mit schlechter Prognose. Dennoch zeigen kürzlich publizierte Studien ermutigende Ergebnisse mit verbesserten Überlebensraten. Es ist jedoch unklar, ob diese Ergebnisse auf die klinische Routine übertragbar sind. Diese retrospektive monozentrische Studie wurde durchgeführt, um Patientencharakteristika und den klinischen Verlauf von Patienten, die innerhalb der multizentrischen German PCNSL Study Group 1-Studie (TRIAL) und außerhalb dieser Studie (R-LIFE) behandelt wurden, zu vergleichen. Insgesamt wurden 93 Patienten mit neu diagnostiziertem PCNSL von November 2000 bis November 2016 ausgewertet. Zwanzig Patienten befanden sich in der TRIAL-Gruppe und 73 in der R-LIFE-Gruppe. Die TRIAL-Patienten waren jünger (medianes Alter 62 Jahre vs. 70 Jahre; p=0,003), hatten einen besseren Allgemeinstatus (ECOG score 0-1: 80.0% vs. 38,4%; p=0,002; medianer Karnofsky-Index: 80% vs. 70%; p=0,003) und waren weniger Hochrisiko-Patienten entsprechend der drei bekannten PCNSL-Prognosesysteme. Das mediane Gesamtüberleben war in der TRIAL-Gruppe länger als im Vergleich zur R-LIFE-Gruppe (33,8 Monate [95% Konfidenzintervall {95%CI} 17,6-50,0] vs. 9,5 Monate [95%CI 3,3-15,7]; p=0,18). In der TRIAL-Gruppe war das progressionsfreie Überleben ebenso besser (25,1 Monate [95%CI 4,7-45,5] vs. 3,7 Monate [95%CI 2,7-4,7]; p=0,13). Die Ergebnisse zeigen, dass ein verbessertes Überleben auf jüngere und „fittere“ Patienten begrenzt ist, die in kontrollierten Studien überrepräsentiert sind.

Schlüsselwörter: primäres ZNS-Lymphom, klinische Routine, klinische kontrollierte Studie, Therapie, Überleben

Documentation

Bibliographic description:

Zeremski, Vanja:

Comparison of the clinical outcome in primary CNS lymphoma patients treated inside and outside of a clinical trial. - 2017, - 71 Pp., 12 Fig., 5 Tbl., 2 App.

Abstract

Primary central nervous system lymphomas (PCNSL) are rare lymphomas with poor prognosis. Yet, recently published studies showed encouraging results with improved survival rates. It is unknown whether these results from controlled trials are applicable to real life settings. This retrospective single-center study was conducted in order to compare the characteristics and clinical outcome of patients treated within the multi-center German Primary CNS Lymphoma Study Group 1 trial (TRIAL) and patients treated outside this trial (R-LIFE). Altogether, 93 consecutive patients with newly diagnosed PCNSL were reported between November 2000 and November 2016 (median age 68 years). Twenty patients were in the TRIAL group and 73 patients in the R-LIFE group. The TRIAL patients were younger (median age 62 years *vs*. 70 years; *p*=0.003), had a better performance status (ECOG score: 0-1: 80.0% *vs.* 38.4%; *p*=0.002; median Karnofsky index: 80% *vs.* 70.0%; *p*=0.003), were less high-risk patients according to all three available PCNSL prognostic scores. Median overall survival in TRIAL group was longer as compared to the R-LIFE group (33.8 months [95% confidence interval {95%CI} 17.6-50.0] *vs*. 9.5 months [95%CI 3.3-15.7]; *p*=0.18). The TRIAL group also reported better progression-free survival (25.1 months [95%CI 4.7-45.5] *vs*. 3.7 months [95%CI 2.7-4.7]; *p*=0.13). These data indicate, that improved survival is limited to young and fit patients, which are usually overrepresented in controlled trials.

Keywords: primary CNS lymphoma, real life, controlled trial, treatment, survival

Table of Contents

Abbreviations

ALC	Absolute lymphocyte count
ASCT	Autologous stem-cell transplantation
Ara-C	Cytarabine
CCI	Charlson Comorbidity Index
CNS	Central nervous system
CSF	Cerebrospinal fluid
CR	Complete response
DLBCL	Diffuse large B-cell lymphoma
EBV	Epstein-Barr virus
ED	Early death
G-PCNSL-SG	German Primary Central Nervous System Lymphoma Study Group
HR	Hazard ratio
HIV	Human immunodeficiency virus
HDC	High-dose chemotherapy
HD-MTX	High-dose methotrexate
IELSG	International Extranodal Lymphoma Study Group
LDH	Lactate dehydrogenase
MSKCC	Memorial Sloan Kettering Cancer Center
MTX	Methotrexate
NHL	Non-Hodgkin Lymphoma
ORR	Overall response rate
OS	Overall survival
PCNSL	Primary central nervous system lymphoma
PFS	Progression-free survival
PR	Partial response
PS	Performance status
R-LIFE	Real-life group
R	Rituximab
SEER	Surveillance, Epidemiology, and End Results Program
SCNSL	Secondary central nervous system lymphoma
SD	Stable disease

TRIAL	Study group
WBRT	Whole-brain radiation therapy
3-F prognostic model	Three-factor prognostic model
95%CI	95% confidence interval

1 Introduction

1.1 Definition, epidemiology and etiology

Central nervous system (CNS) lymphoma is a rare form of non-Hodgkin Lymphoma (NHL) originating in the brain, leptomeninges, spinal cord or intraocular localization of the eyes. The term primary CNS lymphoma (PCNSL) is restricted to CNS lymphoma confined solely to CNS involvement, whereas in a case of secondary CNS Lymphoma (SCNSL) there is concomitant systemic and CNS localization of lymphoma [Villano *et al.* 2011].

PCNSL account approximately 4-6% of all extra-nodal NHL and 1-3% of all newly diagnosed CNS tumors [Villano *et al.* 2011, Dolecek *et al.* 2012]. It is a rare disease, a so-called ultra-orphan disease, with an overall incidence of 0.47 per 100,000 persons per year [Villano *et al.* 2011]. The reported prevalence of PCNSL in Norway was only 10 cases per year [Haldorsen *et al*. 2004]. In the USA, about 450 cases of newly diagnosed PCNSL are registered annually [Shiels *et al.* 2016]. PCNSL affects predominantly older patients, aged 60 years or older. Approximately 50% of all patients are 60 years or older. PCNSL incidence increases with the age, achieving highest rates at above 75 years with an incidence rate 1.9 per 100,000 persons per year [Villano *et al.* 2011]. The incidence rate of PCNSL according to age is shown in Figure 1. In males, a higher incidence as compared to females is reported (0.55 *vs.* 0.39 per 100,000 person-years) [Villano *et al*. 2011].

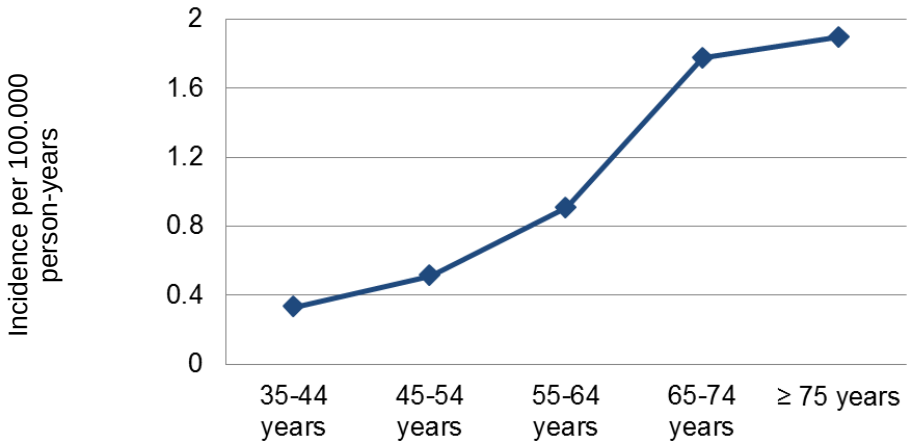


Figure 1. Incidence rates for PCNSL age group; Surveillance, Epidemiology, and End Results Program (SEER) 17 registries research data, 2000–2008 [Villano *et al.* 2011].

The etiology of PCNSL is still unknown. Established risk factors include acquired and/or congenital immunodeficiency conditions. PCNSL is an acquired immunodeficiency syndrome-defining illness associated with low CD4 cell count (<50 cell x10^6/L) and Epstein-Barr virus (EBV) infection. Previously it was reported in 1.6% to 9.0% of patients with human immunodeficiency virus (HIV), yet the introduction of highly active antiretroviral therapy has resulted in decline of the frequency of HIV-associated PCNSL [Shiels *et al.* 2011]. Post-transplant lymphoproliferative disorders involving CNS develop in 1-2% of renal transplant recipients and in 2-7% recipients of heart, lung and liver transplants [Schabet 1999]. CNS post-transplant lymphoproliferative disorders are strongly associated with EBV in the setting of iatrogenic T-cell immunodeficiency induced by agents such as mycophenolate mofetil [Schabet 1999]. Interestingly, in immunocompetent patients with PCNSL, EBV infection is rarely detected, implying different pathogenesis [Schabet 1999].

1.2 Histology and pathogenesis

The majority of PCNSL (90-95%) are histologically classified as diffuse large B-cell lymphomas (DLBCL). The remaining cases are poorly characterized low-grade lymphomas (marginal zone B-cell lymphoma, small lymphocytic B-cell lymphoma), lymphoblastic lymphoma, Burkitt lymphoma and T-cell lymphomas [Ferreri *et al.* 2009, Shiels *et al.* 2016]. Although PCNSL is *per se* defined as NHL, two cases of Hodgkin-PCNSL were also reported in literature [Gerstner *et al.* 2008].

Subclassification of diffuse large B-cell PCNSL as activated B-cell type or germinal B-cell type, analogous to nodal DLBCL, is difficult to apply, due to overlapping features of activated B-cell type and germinal B-cell type. Unlike nodal DLBCL, PCNSL show an activated B-cell immunophenotype, with almost universal expression of MUM-1 (>90% of cases). MUM-1 is a lymphocyte-specific member of the interferon regulatory factor family of transcription factors, which plays a crucial role in cell proliferation, differentiation and survival. It is expressed in final step of intragerminal and in post-germinal (late centrocyte) center B-cell differentiation [Yanai *et al.* 2012]. On the other hand, gene expression profiling implies ongoing germinal center exposure [Philips *et al.* 2014].

Furthermore, PCNSL show high expression of the well-known B-cell lymphoma markers BCL-2, BCL-6, and MYC [Philips *et al.* 2014]. This aggressive biologic

pattern was speculated to underlie the adverse prognosis of PCNSL. Within the CALGB 50202 study the prognostic relevance of BCL-6 and MYC expression was investigated. BCL-6, but not MYC, was shown to correlate with inferior outcome [Rubenstein *et al.* 2013a]. On the other hand, some retrospective analyses found that BCL-6 overexpression correlated with superior outcomes [Levy *et al.* 2008]. Possible explanations for these conflicting findings are heterogeneous treatment approaches, sample size, and variable methodologies or cut-off values of immunohistochemistry [Philips *et al.* 2014].

Recognition of genetic features of PCNSL is difficult due to the rarity of the disease and limited biological material remaining after histologic evaluation. Frequent genomic aberrations in PCNSL are deletion of 6p21, involving the HLA locus, and deletions on chromosome 6q21-6q25. A number of candidate genes are linked to chromosome 6q, including PRDM1, a tumor suppressor which regulates B-cell differentiation, PTPRK, a protein tyrosine phosphatase involved in the regulation of cell adhesion, and A20 (TNFAIP3), a key negative regulator of NFκB signaling, located on 6q23. Other dysregulated signaling pathways of potential significance includes B-cell receptor signaling, with CD79b mutations in 20%, and the JAK/STAT pathway [Philips *et al.* 2014, Ponzoni *et al.* 2014].

Due to a particular gene expression and genomic profile as well as the fact that PCNSL patients are managed with different treatment protocols comparing to nodal DLBCL, PCNSL is recognized as a distinct subtype of DLBCL by the World Health Organization Working Group [Campo *et al.* 2011].

1.3 Localization and clinical presentation

PCNSL tend to present with solitary lesions in two-thirds of cases [Hoang-Xuan *et al.* 2003, Haldorsen *et al.* 2004, Illerhaus *et al.* 2009, Ghesquieres *et al.* 2013]. Multiple/multifocal lesions occur more often in immunocompromised patients. The lesions of PCNSL are primarily located in frontal lobe and periventricular areas involving the thalamus, basal ganglia, and corpus callosum [Haldorsen *et al.* 2004]. Concurrent meningeal involvement is detected in 10-15% of patients, while isolated leptomeningeal lymphoma represent <5% of all PCNSL. Finally, intraocular manifestation, either alone, then referred to as primary intraocular lymphoma, or

often associated with CNS involvement, can occur in nearly 10% of PCNSL cases [Hoang-Xuan *et al.* 2003, Birnbaum *et al.* 2012, Ghesquieres *et al.* 2013].
The localization of PCNSL determines clinical presentation. Initial symptoms include personality and cognitive changes (60%), focal neurologic symptoms (35%), such as hemiparesis, aphasia or headache [Haldorsen *et al.* 2004, Welch *et al.* 2012].

1.4 Prognosis/risk stratification

Prognosis of PCNSL is relatively poor. Various prognostic factors have been identified, that could predict outcome and survival. Advanced age and impaired performance status (PS) have consistently been described as major adverse prognostic factors in PCNSL patients [Abrey *et al.* 1998, Abrey *et al.* 2003, Ferreri *et al.* 2003, Batchelor *et al.* 2003, Langner-Lemercier *et al.* 2016].
Commonly risk stratification is based on two prognostic systems: International Extranodal Lymphoma Study Group (IELSG) score and Memorial Sloan Kettering Cancer Center (MSKCC) score.
IELSG score distinguishes three risk groups based on the presence/absence of five risk factors: age >60 years, ECOG score >1, elevated lactate dehydrogenase (LDH) serum level, elevated cerebrospinal fluid (CSF) protein concentration and involvement of deep structures of the brain (periventricular region, basal ganglia, brainstem and cerebellum). Patients with 0-1, 2-3 or 4-5 of these adverse risk factors had a 2-year overall survival (OS) of 80%, 48% or 15%, respectively [Ferreri *et al.* 2003].
On the other hand, MSKCC score stratifies patients with PCNSL into three risk groups based solely on age and PS. However, in this score, age cut-off is 50 years and PS is classified according to Karnofsky index. Three patient groups are defined: patients <50 years (class 1), patients ≥50 years and Karnofsky index ≥70% (class 2) and patients ≥50 years and Karnofsky index <70% (class 3). Based on these categories, Abrey *et al.* reported significant differences in OS: class 1, 2 and 3 had a median OS of 8.5, 3.2 and 1.1 years, respectively [Abrey *et al.* 2006].
A number of studies have confirmed the prognostic value of IELSG score, especially comparing patients with a score 0-1 and 4-5 [Wieduwilt *et al.* 2012, Birnbaum *et al.* 2012, Kim *et al.* 2014]. The prognostic value of MSKCC score is still debatable. In a study conducted by Madle *et al.* MSKCC score was shown to be predictive for OS

[Madle *et al.* 2015]. On the other hand, other studies failed to prove the prognostic value of MSKCC score regarding OS as well as regarding relapse rate [Birnbaum *et al.* 2012, Schorb *et al.* 2013].

Recently, low absolute lymphocyte count (ALC) was also reported as an independent prognostic factor in PCNSL patients [Jang *et al.* 2016]. Jang *et al.* devised a three-factor (3-F) prognostic model based on age, PS and lymphopenia (defined as ALC ≤875 $x10^6$/L). Assigning 1 point to each factor (ECOG score >1, age >50 years, lymphopenia) patients are classified into three risk groups: low (0 and 1 point), intermediate (2 points), and high (3 points). The 5-year OS rates of the patients in the low-, intermediate-, and high-risk groups were 74.3%, 21.7%, and 12.5%, respectively.

Most recently, our group published a report aiming to validate the 3-F prognostic model in our PCNSL series [Schalk *et al.* 2017]. In this study, 3-F prognostic model failed to stratify patients into risk groups according to survival (OS as well as progression-free survival [PFS]). The influence of lymphopenia (as defined per protocol) on outcome also could not be confirmed.

1.5 Treatment of PCNSL

Therapy strategies have evolved over the last two decades from high-dose methotrexate (HD-MTX)-based chemotherapy with or without whole-brain radiation therapy (WBRT) towards high-dose chemotherapy (HDC) followed by autologous stem-cell transplantation (ASCT) and novel drugs including CD20-antibodies. Due to the rarity of PCNSL and challenges conducting randomized controlled clinical trials in these patients' group data obtained from these studies are limited, resulting in a relative low evidence level to guide therapeutic decisions [Ponzoni *et al.* 2014, Phillips *et al.* 2014]. Therefore, for these patients there is no well-defined standard of care [NCCN 2016].

1.5.1 Surgery

The role of surgery in PCNSL is restricted to obtaining a histopathologic diagnosis by stereotactic brain biopsy. Aggressive tumor resection is not indicated due to

increased risk of postoperative neurological deficit. More importantly, it did not result in improved survival [Bataille *et al.* 2000, Bellinzona *et al.* 2005].

However, a study published by the German Primary Central Nervous System Lymphoma Study Group (G-PCNSL-SG) has challenged this traditional view. Results of this randomized, phase III study showed that in selected cases (e.g. in a case of single lesions) aggressive tumor resection could improve PFS [Weller *et al.* 2012]. Moreover, these results were independent of age and PS. Therefore, in individualized cases aggressive surgical tumor reduction could be taken in consideration as that may lead to immediate relief of tumor mass effect, rapid termination of corticosteroid therapy and elimination of cell populations with drug resistance potential [Rubenstein *et al.* 2013b].

1.5.2 Whole-brain radiation therapy

PCNSL are radiosensitive tumors and respond well to radiation therapy. Due to multifocal und infiltrative disease nature, WBRT was advocated [Shibamoto *et al.* 2003]. WBRT alone leads to high response rates (overall response rate [ORR] 90%), yet is followed by frequent and rapid relapse [Nelson 1999, Shibamto *et al.* 2003]. The addition of WBRT to chemotherapy initially showed promising results [DeAngelis *et al.* 2002, Gavrilovic *et al.* 2006, Shah *et al.* 2007]; however, it was associated with disabling neurotoxicity (incontinence, gait, memory disturbance, etc.) and 30% therapy-related mortality [Abrey *et al.* 1998]. Thiel *et al.* conducted a randomized, phase III, non-inferiority trial of chemotherapy (HD-MTX plus ifosfamide) with or without WBRT in PCNSL patients. Results showed no difference in OS, yet significant difference was demonstrated regarding neurotoxicity for patients who received WBRT [Thiel *et al.* 2010].

As a result, WBRT is currently omitted in the first-line PCNSL therapy and applied solely in palliative or salvage settings [Thiel *et al.* 2010].

Whether other forms of radiation therapy (partial brain radiation therapy, reduced dose WBRT, etc.) may play a role in PCNSL treatment is yet to be seen. Iwabuchi *et al.* compared outcome in PCNSL patients receiving HD-MTX-containing chemotherapy and WBRT with outcome in PCNSL patients receiving HD-MTX-containing chemotherapy and partial brain radiation therapy. No significant difference was reported, neither for relapse rate nor regarding neurotoxicity [Iwabuchi *et al.*

2016]. Morris *et al.* reported that reduced dose WBRT following chemotherapy could be associated with long-term disease control and minimal neurotoxicity [Morris *et al.* 2013]. Clearly, further studies are needed to evaluate the possible advantages of these forms of radiation therapy.

1.5.3 Chemotherapy

HD-MTX constitutes the backbone of PCNSL treatment. As a single agent, and when administered without WBRT, the most frequently used methotrexate (MTX) dose was 3.5-8 g/m^2 [Guha-Thakurta *et al.* 1999, Batchelor *et al.* 2003; Zhu *et al.* 2009, Thiel *et al.* 2010, Cobert *et al.* 2010]. Regarding the fact that 4-6 cycles of HD-MTX are necessary for achieving remission, administration of 6-8 cycles has been considered as standard of care [Batchelor *et al.* 2003, Zhu *et al.* 2009, Cobert *et al.* 2010]. With this approach complete remission (CR) was achieved in the majority of patients with prolonged survival rates comparing to WBRT alone (2-year OS 50-70%) [Guha-Thakurta *et al.*1999, Batchelor *et al.* 2003, Herrlinger *et al.* 2005; Zhu *et al.* 2009, Thiel *et al.* 2010, Cobert *et al.* 2010]. Interestingly, therapy response was reported not to be dose dependent (reported CR rates: 58% *vs.* 50% in patients treated with MTX 8 g/m^2 or 3.5 g/m^2, respectively) [Cobert *et al.* 2010]. HD-MTX monotherapy was associated with acceptable rates of myelosuppression, reversible renal insufficiency and acceptable neurotoxicity. Furthermore, this treatment option is also feasible in elderly patients [Zhu *et al.* 2009, Welch *et al.* 2012]. However, the issue concerning rapid relapse was not solved given that only 20% of patients achieved long-term PFS [Batchelor *et al.* 2003]. In recent years, HD-MTX was combined with numerous additional drugs in order to improve outcomes of HD-MTX monotherapy (Appendix Table 1 and 2).

Ferreri *et al.* conducted the first randomized phase III study (IELSG 20 trial) on 79 patients with PCNSL comparing the role of HD-MTX plus cytarabine (Ara-C) *vs.* HD-MTX alone [Ferreri *et al.* 2009]. This study demonstrated significant improvement in PFS comparing to HD-MTX monotherapy, however no difference in OS was reported (3-year OS 46% *vs.* 32%; p=0.07). On the other hand, adverse events, especially infectious complications, hepatotoxicity and hematological toxicities, were reported more often in patients undergoing HD-MTX therapy combined with Ara-C.

Currently, the anti-CD20 monoclonal antibody rituximab (R) is frequently combined with single-agent HD-MTX or MTX-based polychemotherapy, based on the observations that addition of rituximab could improve not only response rates, but also OS rates [Chamberlain *et al.* 2010, Fritsch *et al.* 2011, Holdhoff *et al.* 2014, Ly *et al.* 2016].

One of the most promising approaches in treatment of PCNSL is HDC with subsequent ASCT. Various conditioning therapies have been used including a combination of thiotepa with busulfan or carmustine or the BEAM regimen (carmustine, etoposide, Ara-C, melphalan) [Abrey *et al.* 2003, Schorb *et al.* 2013, Omuro *et al.* 2015a]. Omuro *et al.* assessed induction chemotherapy with R, MTX, procarbazine, and vincristine, followed by consolidation with thiotepa, cyclophosphamide und busulfan. Results showed impressive response rates and moreover excellent disease control (OS not reached at 45 months; 2 year PFS 79%) [Omuro *et al.* 2015a]. However, a recently published study by Scordo *et al.* showed that this therapy regimen was associated with high toxicity burden [Scordo *et al.* 2017]. The most common non-hematological toxicities grade ≥3 were febrile neutropenia (95% of patients) and mucositis (81% of patients). Fifteen percent of patients experienced clinically relevant ≥3 non-hematological toxicities, and 7% of patients died of treatment-related toxicity.

The above-mentioned high-dose chemotherapeutic strategies appear to be highly effective, yet associated with high toxicity burden. Furthermore, it cannot not be ignored, that these chemotherapeutic protocols are given to young and fit patients, a subgroup that constitutes a minority of PCNSL patients, only.

1.6 Controlled trials in cancer patients

A number of controlled trials have shown that modern therapy approaches in PCNSL result in improved survival rates [Ferreri *et al.* 2009, Holdhoff *et al.* 2014, Omuro *et al.* 2015a]. Yet outcome in “real-life” settings demonstrates less favorable results. This observation poses the question whether results from controlled trials in PCNSL are referable to the “real-life” setting outside controlled clinical trials.

Controlled trials have an important role in modern medicine and they guide clinical practice. However, it should be considered, that controlled trials are conducted under standardized conditions and in selected groups of patients often far from daily clinical

practice. Narrow eligibility criteria may result in highly selected patient populations, thereby threatening the overall generalizability of study findings to the “real-life” setting.

Mitchell *et al.* conducted a retrospective study comparing “real-life” metastatic renal cell carcinoma patients with controlled trial patients [Mitchell *et al.* 2014]. Results showed that “real-life” patients are significantly older (mean 4.6 years older than clinical trial patients) and sicker (“real-life” patients had a significant poorer risk disease by MSKCC score – poor: 7.4% *vs.* 2.9%; favorable: 31% *vs.* 44% – and were more likely to have impaired functional status [ECOG score >1: 8.4% *vs.* 0.6%]) than those patients enrolled in controlled trials. Similar results were reported in patients with acute myeloid leukemia [Wang *et al.* 2015] and colon carcinoma [Mol *et al.* 2013].

Furthermore, Mol *et al.* reported a significantly worse outcome in non-trial patients with colon carcinoma. Interestingly, no difference in survival was observed when patients with comparable baseline characteristics (including age, PS) were treated within and outside controlled trials. Thus, the influence of standardized treatment on survival rates could be eliminated [Mol *et al.* 2013].

To the best of our knowledge, previously, it was not reported, whether the encouraging data from controlled clinical trials in PCNSL are transferable to “real-life” or are solely limited to controlled trials. In order to answer this question, characteristics and clinical outcome of PCNSL patients treated within and outside a controlled trial were investigated in this dissertation.

1.7 Aim of the study

1.7.1 Primary study objectives

The primary objectives of this study were:

- To compare clinical characteristics of patients with PCNSL treated within a controlled clinical trial (G-PCNSL-SG-1; TRIAL group) with patients treated outside this trial (R-LIFE group);
- To compare clinical outcome of both patient populations (TRIAL *vs*. R-LIFE).

1.7.2 Secondary study objectives

Secondary objectives of this study were:

- To compare the outcome of this PCNSL cohort with survival data obtained in other retrospective and prospective PCNSL trials;
- To investigate the influence of “pro-active” follow-up on survival data;
- To validate available prognostic scores for PCNSL;
- To identify early death (ED) in PCNSL and patients at risk of ED.

2 Patients and Methods

2.1 Study design

This single-center, non-interventional study was conducted in patients with newly diagnosed PCNSL treated consecutively between November 2000 and November 2016 in the Department of Hematology and Oncology, University Hospital Magdeburg. The study was retrospective up to June 2014 and prospectively documented from then onwards.
It included two patient populations:

- Patients treated within the multi-center G-PCNSL-SG-1 trial [Thiel *et al.* 2010, Korfel *et al.* 2015] (TRIAL group);
- Patients treated outside of this controlled trial (R-LIFE group). Patients with NHL manifestation outside the CNS or patients with SCNSL were excluded from this analysis.

2.1.1 TRIAL group

The TRIAL group was composed of patients treated within the G-PCNSL-SG-1 trial. The G-PCNSL-SG-1 trial was a national, randomized, multi-center (75 centers, 551 patients), phase III, controlled trial conducted between May 2000 und May 2009 in patients with newly PCNSL. Of 551 patients who entered the study, 318 were treated per-protocol (57.7%). The major protocol deviations were as follows: death during chemotherapy (*n*=66), omission of WBRT in patients assigned to first-line chemotherapy plus WBRT (*n*=49), failure to achieve CR (*n*=44), lost to follow-up (*n*=27). The study was designed to answer the question whether the omission of WBRT from the treatment of newly diagnosed PCNSL compromises OS. The G-PCNSL-SG-1 trial was registered with ClinicalTrials.gov number NCT00153530.

2.1.1.1 G-PCNSL-SG-1 trial inclusion and exclusion criteria

G-PCNSL-SG-1 trial inclusion criteria were as follows:

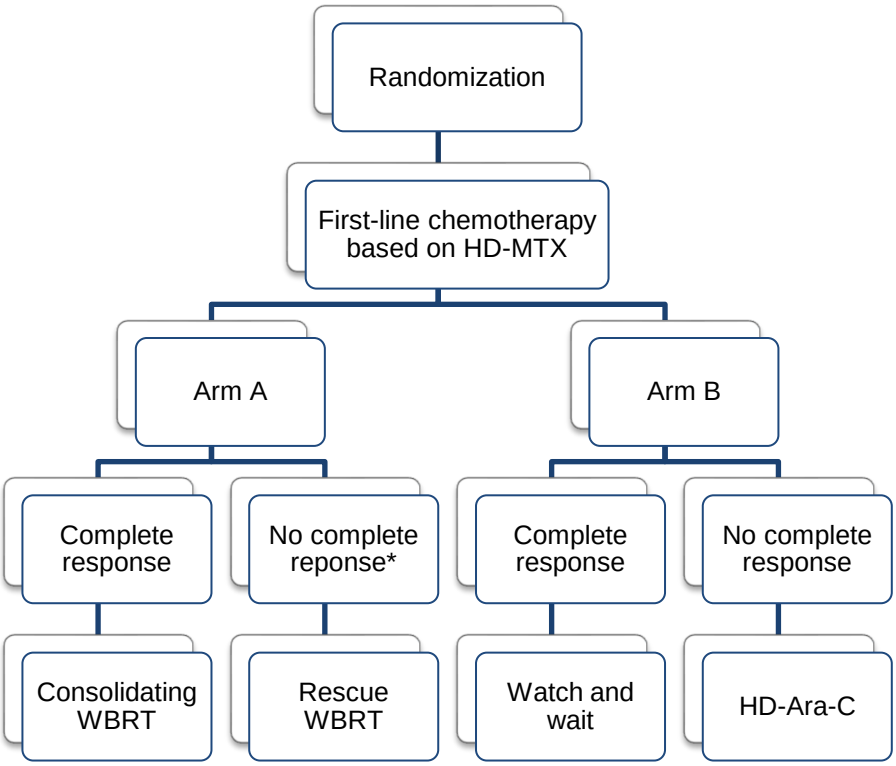
- Newly diagnosed PCNSL (histologically or cytologically/immunocytologically confirmed);
- Age ≥18 years;
- Life expectancy of at least 2 months;
- Adequate bone marrow reserve with a peripheral granulocyte count of >1.5 $x10^6$/L and thrombocyte count of >100 $x10^6$/L; bilirubin in the normal range; glutamic-oxaloacetic transaminase of <3 times the upper normal limit and adequate renal function with a creatinine clearance of >50 mL/min and serum creatinine in the normal range.

G-PCNSL-SG-1 trial exclusion criteria were as follows:

- Manifestation of lymphoma outside of the CNS;
- Severe diseases in other organs which would make application of intensive chemotherapy impossible;
- Karnofsky index <50% due to previous diseases other than PCNSL (Karnofsky index <30% only due to the PCNSL);
- Active infection;
- HIV positivity;
- Previous treatment of PCNSL other than with corticosteroids, antiepileptics or diuretics;
- Previous radiation therapy of the brain;
- Concomitant or previous malignant diseases in the last 5 years except for an adequately treated basal cell carcinoma or cervical carcinoma *in situ*;
- Immunosuppression, concomitant immunosuppressive therapy, or organ transplantation;
- Ongoing chemotherapy for another disease.

2.1.1.2 G-PCNSL-SG-1 trial treatment

Patients were randomised in a 1:1 ratio to receive first-line chemotherapy based on HD-MTX with or without subsequent WBRT (Figure 2).



*No complete response: partial response, stabile disease, and progressive disease.

Figure 2. G-PCNSL-SG-1 trial design [Thiel *et al.* 2010]. HD-MTX: high-dose methotrexate; WBRT: whole-brain radiation therapy; HD-Ara-C: high-dose cytarabine.

From 2000 until 2006 all patients received intravenous HD-MTX (4 g/m^2 over 4 hours) on day 1 of six bi-weekly cycles, as first-line chemotherapy. In May 2006 a protocol amendment was made due to low CR rates and presumption that HD-MTX alone is insufficient. Ifosfamide was added to the first-line chemotherapy. From May 2006 onwards received all patients HD-MTX plus ifosfamide (1.5 g/m^2 over 3 hours) on days 3-5 of six bi-weekly cycles. In those patients assigned to receive first-line chemotherapy following WBRT, it was applied to a total dose of 45 Gy, in 30 fractions à 1.5 Gy. Patients assigned to receive first-line chemotherapy without WBRT who

had not achieved complete response were given intravenous high-dose Ara-C (3 g/m^2 over 3 hours) every 12 hours for 2 days.

The G-PCNSL-SG-1 trial was approved by local ethics committee from each participating center and informed consent was obtained from each participant (Ethics Committee of Otto-von-Guericke University Magdeburg, Medical Faculty approval 29.01.2001, protocol number: 184/00).

2.1.2 R-LIFE group

R-LIFE group was composed of patients treated outside the G-PCNSL-SG-1 trial. These patients were not enrolled in the study, because they did not meet the inclusion criteria, patients' wish, physicians' decision or because the study recruitment was already closed at the time of PCNSL diagnosis.

2.1.2.1 R-LIFE treatment

Patients in the R-LIFE group received HD-MTX alone as a first-line chemotherapy (up to six bi-weekly courses; 4 g/m^2); which was at that time considered as standard of care in this institution. In cases of impaired renal function, HD-MTX dose was reduced up to 50% or Ara-C was administered as the first-line therapy (up to four tri-weekly courses; 12 g/m^2 as above described). From December 2015 onwards patients received R-MTX as first-line chemotherapy, due to encouraging results from recently published studies with rituximab [Chamberlain *et al.* 2010, Fritsch *et al.* 2011, Holdhoff *et al.* 2014, Ly *et al.* 2016].
Consolidation therapy as WBRT or HDC with ASCT was not applied in these patients.
Patients not eligible for chemotherapy (due to comorbidity, low PS) received WBRT or dexamethasone monotherapy with palliative intention at the discretion of the treating physician.
For these patients, written informed consent for this analysis was not obtained due to the mainly retrospective and non-interventional study. All procedures were performed in accordance with the general ethical principles outlined in the Declaration of Helsinki [WMA 2013].

2.2 Analyzed variables

Data were collected by reviewing patients' medical records.
The following data were collected:

- Demographic variables: age, sex;
- Time-points: date of surgery and histological diagnosis, time of death, last follow-up;
- Laboratory variables: baseline ALC, LDH and creatinine clearance as calculated by the Cockgroft-Gault method;
- Clinical variables: number and localization of tumor lesions, histology type, Karnofsky index, ECOG score, Charlson Comorbidity Index (CCI) [Charlson *et al.* 1987], MSKCC prognostic score [Abrey *et al.* 2006], IELSG prognostic score [Ferreri *et al.* 2003], 3-F prognostic model [Jang *et al.* 2016];
- Treatment-related variables: type of therapy, therapy dosage, number of therapy cycles;
- Outcome: CR, partial response (PR), mixed response (MR), stabile disease (SD), progressive disease, PFS, OS, relapse.

2.3 Definitions

OS was defined as the time between histological diagnosis and death or loss to follow-up. PFS was defined as the time between histological diagnosis and progress, relapse or death. Data for patients without an event were censored at the time of the last contact (telephone or visit).
ORR rate was defined as the sum of CR and PR. Response to therapy was determined by contrast-enhanced computed tomography or magnetic resonance tomography [Abrey *et al.* 2005, Thiel *et al.* 2010].
The term "pro-active" follow-up describes additional follow-up phone calls to primary care physicians and patients' families for all patients known to be alive in the last data base entry. This was performed in order to get more accurate information regarding survival and course of the disease.
ED was defined as death within 4 months from histological diagnosis [Bairey *et al.* 2013].

2.4 Review of retrospective and prospective PCNSL studies

In the Appendix Table 1 und 2, the type and outcome of administered therapy regimens from published, retrospective and prospective PCNSL studies were summarized. Keywords for the literature search were “CNS lymphoma” and “treatment”; inclusion criteria for consideration were English-speaking studies on adult patients with newly PCNSL, which were published between January 2010 and November 2015.

2.5 Statistical analysis

Categorical variables were compared using X^2 statistic or Fisher’s exact test, where applicable. Continuous variables were compared using Wilcoxon-Mann-Whitney test. The Kaplan-Meier method was used for survival analysis [Kaplan *et al.* 1958], with assessment of differences by the log-rank test. The Cox proportional hazards model was used to calculate the hazard ratio (HR). Survival rates were derived from the Kaplan-Meier estimates. The median follow-up time was derived from “reverse” Kaplan-Meier estimates [Shuster 1991]. Two-sided p values <0.05 were considered statistically significant. Statistical analyses were carried out using SPSS version 24 and Microsoft Excel version 14.7.1.

3 Results

3.1 Patient characteristics

Altogether, 107 patients were identified with newly diagnosed CNS lymphoma treated consecutively between November 2000 and November 2016 in the Department of Hematology and Oncology, University Hospital Magdeburg. Fourteen patients with SCNSL were excluded from this study, remaining 93 patients with PCNSL for this study analysis. Enrollment and analysis of the study population is shown in Figure 3.

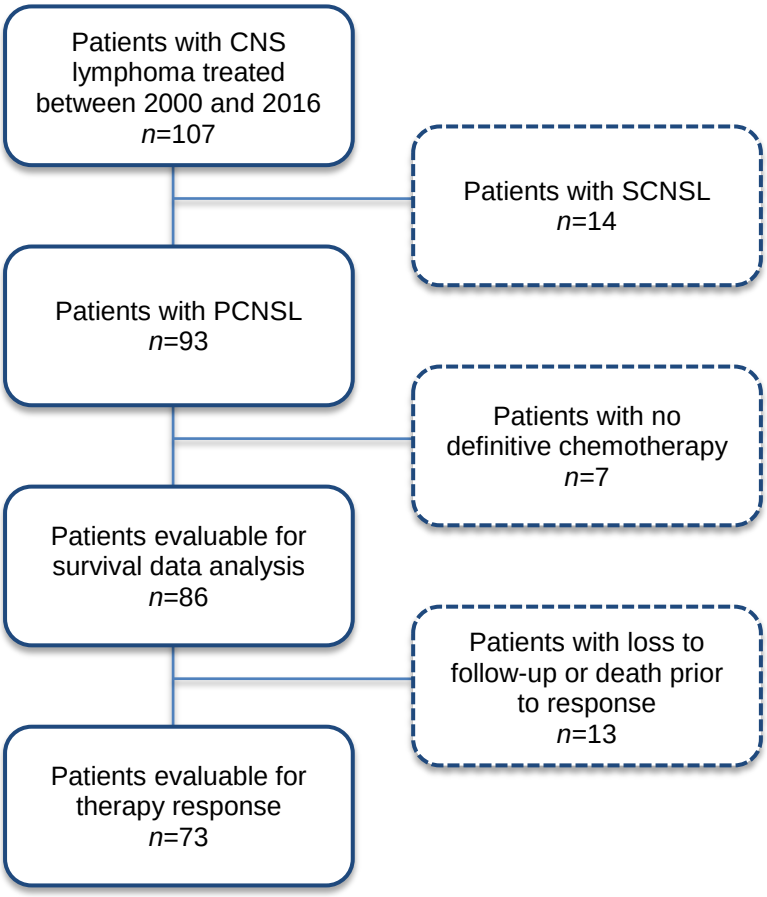


Figure 3. Enrollment and analysis of the study population. CNS: central nervous system; SCNSL: secondary CNS lymphoma; PCNSL: primary CNS lymphoma.

Twenty (21.5%) patients were treated within the G-PCNSL-SG-1 trial (TRIAL group) and 73 patients (78.5%) were treated outside the clinical trial (R-LIFE group). In the time period when the G-PCNSL-SG-1 trial was active in this center, 19 patients were not included in this trial. Given the retrospective character of this analysis, there is no

information available for the reasons pro or contra the participation in the G-PCNSL-SG-1 trial. Thirteen out of these 19 patients were probably not eligible for chemotherapy (age ≥70 years, ECOG sore ≥3, Karnofsky index ≤60% or CCI >4).

Of the 93 patients with PCNSL, 47 (50.5%) were men and 46 (49.5%) women. Median age of the total patient population was 68 years (range 23-83 years), whereas 42 patients (45.2%) were aged 70 years or older.

Minimum CCI score in all patients was 2, due to the 2 points given for lymphoma diagnosis per patient. A CCI of 2 was present in 24 patients (25.8%), CCI 3-4 in 46 patients (49.8%), and CCI ≥5 in 23 patients (24.7%). Forty-four patients (47.3%) had ECOG score 0-1. Forty-nine patients (52.7%) had a solitary lesion and forty-four patients (47.3%) had ≥2 lesions.

Distribution of MSKCC score was as follows: class 1 in 13 patients (13.9%), class 2 in 43 patients (46.2%) and class 3 in 37 patients (39.8%).

The IELSG score was 0-1 in 22 patients (23.6%), 2-3 in 55 patients (59.1%) and 4 in 16 patients (17.2%). Due to missing data on CSF protein level, the maximum IELSG score in all patients was 4.

According to the 3-F-prognostic model, 37 patients (39.8%) were low-risk, 36 patients (38.7%) intermediate-risk and 20 patients (21.5%) were high-risk.

Histology revealed aggressive B-NHL in the great majority of patients (89 patients; 95.7%). T-NHL was diagnosed in 3 patients and indolent NHL in 1 patient.

Patients' characteristics and comparison between the R-LIFE group and the TRIAL group are given in Table 1.

Table 1. Comparison of patients' characteristics of TRIAL and R-LIFE group

Parameter	Total *n*=93	TRIAL group *n*=20	R-LIFE group *n*=73	*p* value
Age, median	68 years	62 years	70 years	0.003
Range	23-83 years	44-75 years	23-83 years	
≥70 years	42 (45.2%)	3 (15.0%)	39 (53.4%)	0.004
CCI score[a]				
2	24 (25.8%)	4 (20.0%)	20 (27.4%)	0.58
3-4	46 (49.5%)	11 (55.0%)	35 (47.9%)	0.62
≥5	23 (24.7%)	5 (25.0%)	18 (24.6%)	1.0
Performance status				
ECOG score				
0-1	44 (47.3%)	16 (80.0%)	28 (38.4%)	0.002
2-4	49 (52.7%)	4 (20.0%)	45 (61.6%)	0.002
Karnofsky index, median	70%	80%	70%	0.003
Number of lesions				
Solitary lesion	49 (52.7%)	14 (70.0%)	35 (47.9%)	0.13
Multiple lesions[b]	44 (47.3%)	6 (30.0%)	38 (52.1%)	0.13
MSKCC score				
1	13 (13.9%)	5 (25.0%)	8 (10.9%)	0.14
2	43 (46.2%)	11 (55.0%)	32 (43.8%)	0.45
3	37 (39.8%)	4 (20.0%)	33 (45.2%)	0.07
IELSG score[c]				
0-1	22 (23.6%)	9 (45.0%)	13 (17.8%)	0.02
2-3	55 (59.1%)	10 (50.0%)	45 (61.6%)	0.44
4	16 (17.2%)	1 (5.0%)	15 (20.5%)	0.18
Individual parameters[d]				
Age >60 years	67 (72.0%)	11 (55.0%)	56 (76.7%)	
ECOG score >1	49 (52.7%)	4 (20.0%)	45 (61.6%)	
LDH elevated	52[e] (53.8%)	12 (60.0%)	40[e] (56.3%)	
Localization: Deep brain region	51 (54.8%)	8 (4.0%)	43 (58.9%)	
3-F prognostic model				
Low	37 (39.8%)	15 (75%)	22 (30.1%)	0.22
Intermediate	36 (38.7%)	3 (15%)	33 (45.2%)	0.02
High	20 (21.5%)	2 (10%)	18 (24.7%)	0.001

Abbreviations: CCI: Charlson Comorbidity Index [Charlson *et al.* 1987], MSKCC score: Memorial Sloan Kettering Cancer Centre prognostic score [Abrey *et al.* 2006], IELSG score: International Extranodal Lymphoma Study Group prognostic score [Ferreri *et al.* 2003], LDH: lactate dehydrogenase; 3-F prognostic model: three-factor prognostic model [Jang *et al.* 2016].

[a] Includes 2 points given for lymphoma diagnosis per patient;

[b] ≥ 2 lesions;

[c]1 point for elevated cerebrospinal fluid protein level could not be attributed (data not available); therefore the maximal IELSG score was 4;
[d]Descriptive only;
[e]Value not available for 2 patients.

3.2 Treatment

Definitive chemotherapy was applied in 86 patients, whereas 5 patients received dexamethasone monotherapy and 2 patients WBRT only (the latter patients were all from the R-LIFE group).
HD-MTX monotherapy was applied as first-line treatment in the great majority of the patients (*n*=76; 86.4%). All patients within the TRIAL group received HD-MTX monotherapy; additional WBRT was applied in 64.7% of patients (11/17 patients with response evaluation after HD-MTX). Neither of TRIAL patients received ifosfamid/HD-MTX considering that the last patient recruitment was before protocol amendment as described above.
In R-LIFE group 84.8% (56/66) patients were treated with HD-MTX in first-line. Other treatments were R-MTX (*n*=5; 7.6%), Ara-C (*n*=4; 6.1%) and polychemotherapy (*n*=1; 1.5%).

3.3 Response

From altogether 86 patients who received definitive chemotherapy, 73 could be evaluated for therapy response. In 13 patients (15.1%), no response data were available due to loss to follow-up or death prior to response evaluation.

ORR was achieved in 44 patients (60.3%). CR was observed in 22 patients (30.1%), PR also in 22 patients (30.1%), whereas MR was reported in 1 (1.4%) patient. Progressive disease was reported in 23 patients (31.5%) and SD in 5 patients (8.8%). Therapy response of the entire PCNSL cohort is shown in Figure 4.

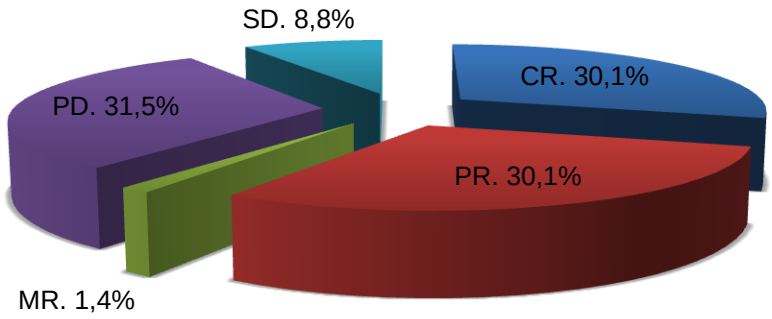


Figure 4. Treatment response of the entire PCNSL cohort (*n*=73). CR: complete response; PR: partial response; PD: partial disease; SD: stabile disease; MR: mixed response.

3.4 Survival

Median follow-up of the entire study population was 112.6 months (95% confidence interval [95%CI] 81.9-143.3). Sixty-three patients (73.3%) died and 23 patients (26.7%) are alive. In the entire cohort the median OS was 13.3 months (95%CI 0-27.5), as shown in Figure 5.

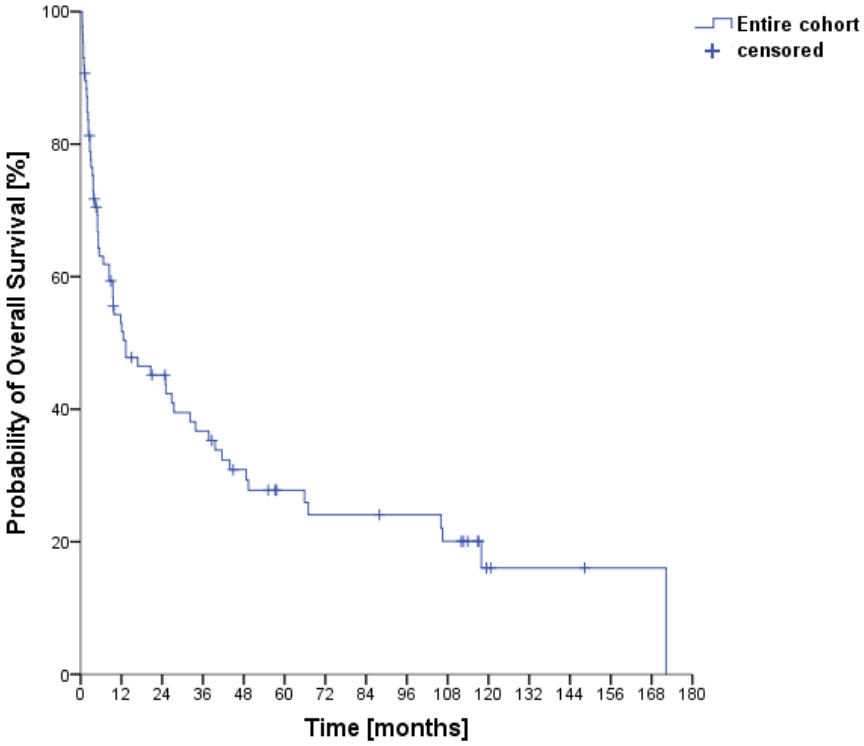


Figure 5. Overall survival in entire PCNSL cohort (median 13.3 months) (*n*=86).

Median OS was 33.8 months (95%CI 17.6-50.0) in the TRIAL group compared to only 9.5 months (95%CI 3.3-15.7) in the R-LIFE group (p=0.18), as shown in Figure 6. This resulted in HR of 0.67 ([95%CI 0.38-1.20]; p=0.18).

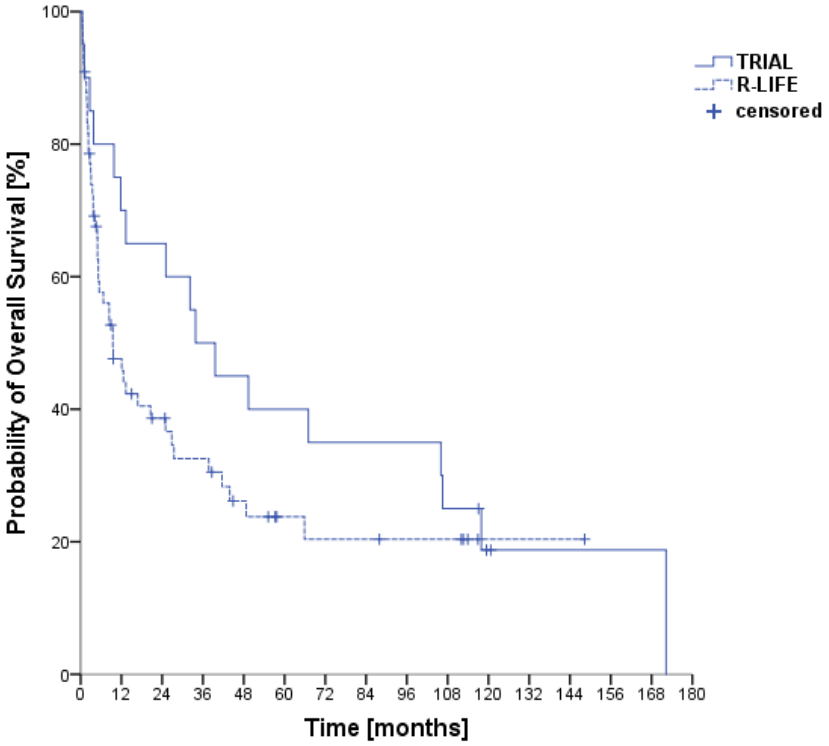


Figure 6. Overall survival for patients treated within the G-PCNSL-SG-1 trial (TRIAL group) and for patients treated within the ”real-life“ setting (R-LIFE group) (median 33.8 months *vs.* 9.5 months).

The OS rates for the entire cohort were 45.2% (95%CI 34.4-56.0) at 2 years and 27.8% (95%CI 17.6-38.0) at 5 years.

When analyzing the TRIAL and R-LIFE groups separately, a significant difference was observed: OS at 2 years was 65.0% and 38.6%, respectively; OS at 5 years was 40.0% and 23.8% respectively. In Table 2, 2-year OS and 5-year OS for the TRIAL and R-LIFE groups are shown.

Table 2. Comparison of 2-year OS and 5-year OS for the TRIAL and R-LIFE groups

	TRIAL group	R-LIFE group	*p* value
2-year OS (95%CI)	65.0% (44.0-86.0)	38.6% (26.5-50.9)	0.01
5-year OS (95%CI)	40.0% (18.4-61.6)	23.8% (12.2-35.4)	0.01

Abbreviations: OS overall survival; 95%CI 95% confidence interval.

The median PFS in the entire study population was 4.2 months (95%CI 0-10.0), as shown in Figure 7.

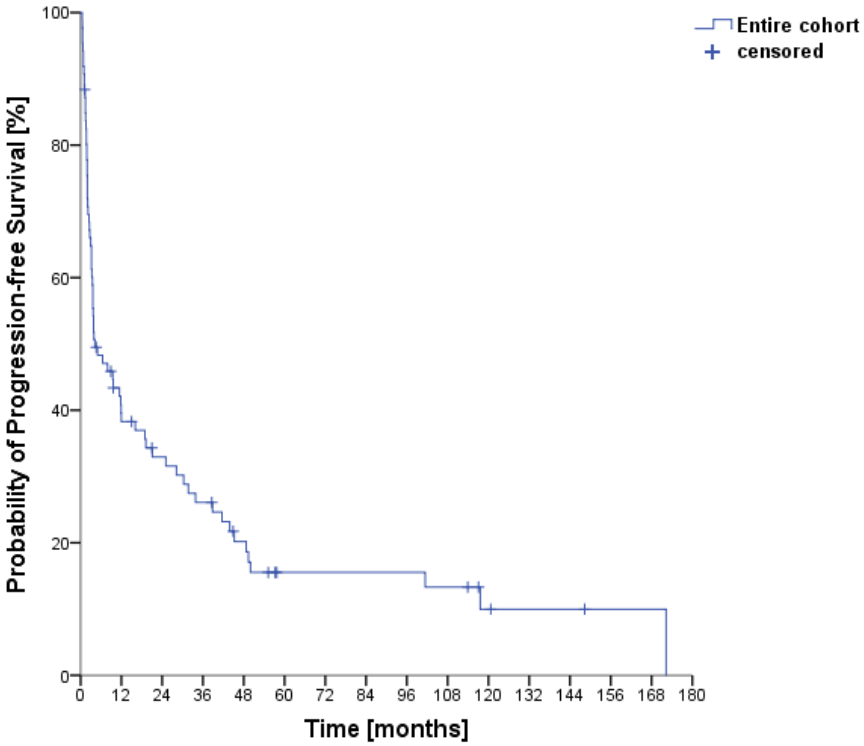


Figure 7. Progression-free survival for entire PCNSL cohort (median 4.2 months) (*n*=86).

Analyzing the TRIAL group und the R-LIFE group separately showed that the median PFS in the TRIAL group was 25.1 months (95%CI 4.7-45.5) as compared to only 3.7 months (95%CI 2.7-4.7) in the R-LIFE group (p=0.13). The respective HR was 0.66 ([CI95% 0.37-1.15]; p=0.14). PFS for TRIAL and R-LIFE group are shown in Figure 8.

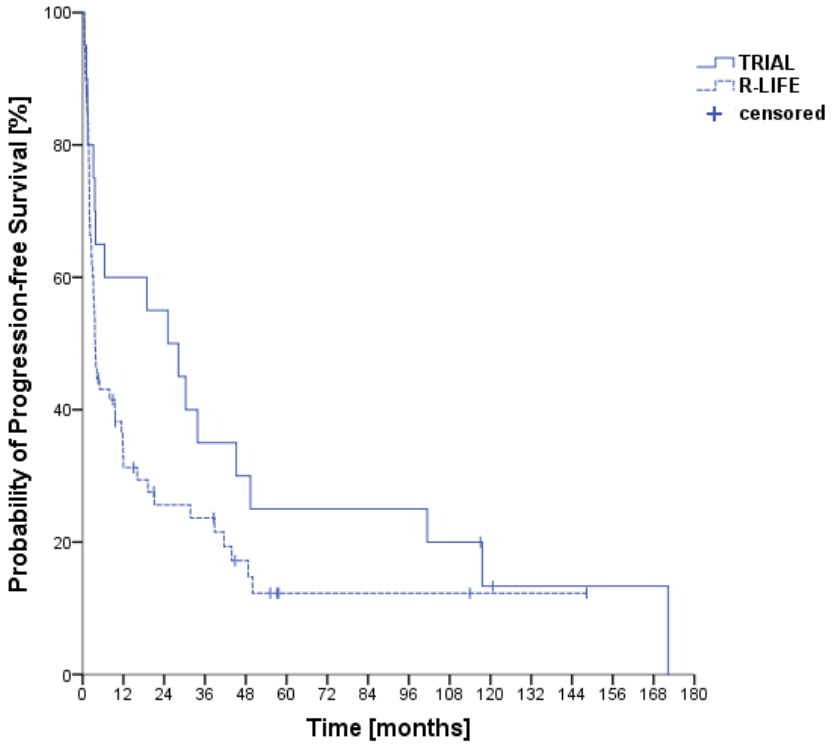


Figure 8. Progression-free survival for patients treated in the G-PCNSL-SG-1 trial (TRIAL group) and for patients treated in the ”real-life“ setting (R-LIFE group) (25.1 months *vs.* 3.7 months).

The PFS rates at 2 years were 33.0% (95%CI 22.8-43.2) and 15.5% (95%CI 7.1-23.9) at 5 years, respectively. In the TRIAL group, PFS at 2 years was 55.0% and at 5 years 25.0%. In the R-LIFE group, PFS at 2 year was 25.6% and 12.3% at 5 years. In Table 3, 2-year PFS and 5-year PFS for the TRIAL and the R-LIFE group are shown.

Table 3. Comparison of 2-year PFS and 5-year PFS for TRIAL and R-LIFE groups

	TRIAL group	R-LIFE group	*p* value
2-year PFS (95%CI)	55.0% (33.2-76.8)	25.6% (14.4-36.8)	0.007
5-year PFS (95%CI)	25.0% (6.0-44.0)	12.3% (3.1-21.5)	0.01

Abbreviations: PFS progression-free survival; 95%CI 95% confidence interval.

3.5 "Pro-active" follow-up

In the period from November 2000 until November 2014, altogether 75 patients with newly diagnosed PCNSL were identified (87.2% of all patients evaluated for survival data). Initially, data were collected according to standard follow-up, regarding OS. From November 2014 until November 2016 a "pro-active" follow-up was conducted (Figure 9).

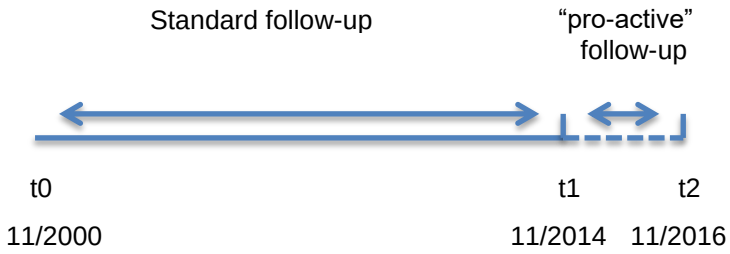


Figure 9. Time flow-chart of patients according to follow-up.

Median follow-up with standard follow-up was 26.4 months with a low event rate (deaths; 38.7%), whereas median follow-up with "pro-active" follow-up was 112.6

months. Event-rate with “pro-active” follow-up was significantly higher (72.0%). Survival data according to type of follow-up are shown in Table 4.

Table 4. Comparison of standard and “pro-active” follow-up

	Standard follow-up	“Pro-active” follow-up	*p* value
Follow-up median (95%CI)	26.4 months (9.7-43.1)	112.6 months (82.0-143.2)	<0.001
Events	29 (38.7%)	54 (72.0%)	<0.001
OS median (95%CI)	39.6 months (6.3-72.9)	25.0 months (10.6-39.4)	0.11

Abbreviations: 95%CI 95% confidence interval; OS overall survival.

3.6 Impact of prognostic scores and comorbidity index on survival

All three prognostic scores successfully discriminated risk groups according to OS, but not, however, to PFS. The median OS of patients allocated to the low-risk group ranged from 26.8 months (according to 3-F prognostic model) to 67.0 months (according to MSKCC score). Reported median OS for high-risk patients ranged only from 3.5 months to 3.8 months. OS and PFS for patient subgroups according to IELSG, MSKCC and 3-F prognostic model score are shown in Figures 10,11 and 12 and in Table 5.

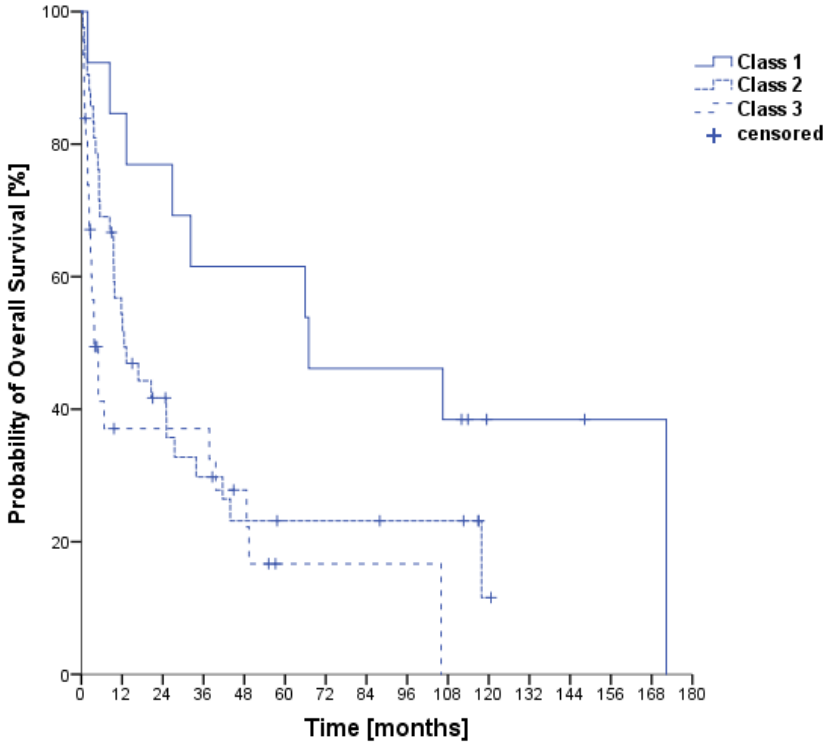


Figure 10. Overall survival for patients according to MSKCC prognostic score.

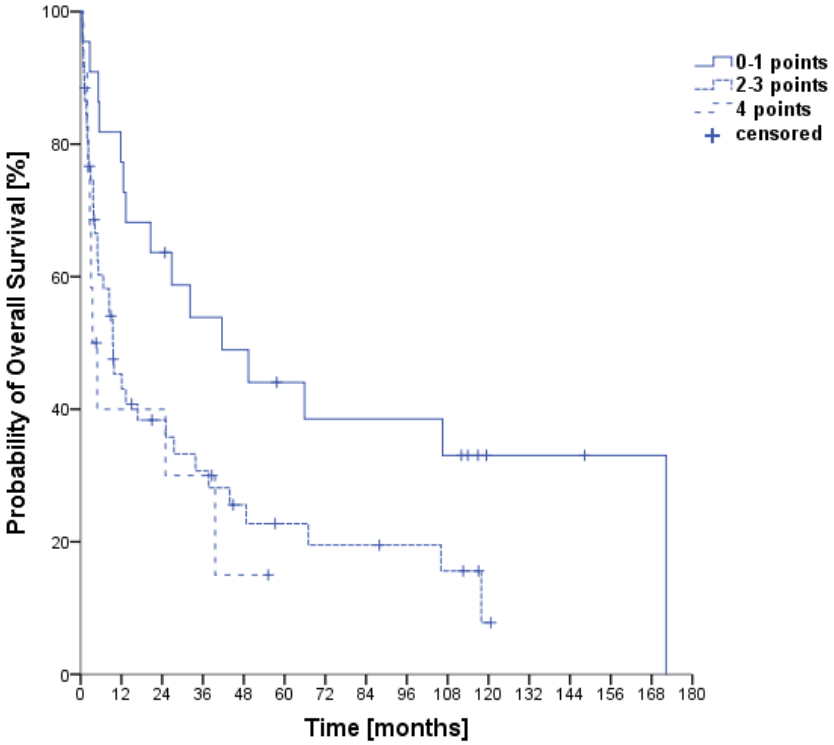


Figure 11. Overall survival for patients according to IELSG prognostic score.

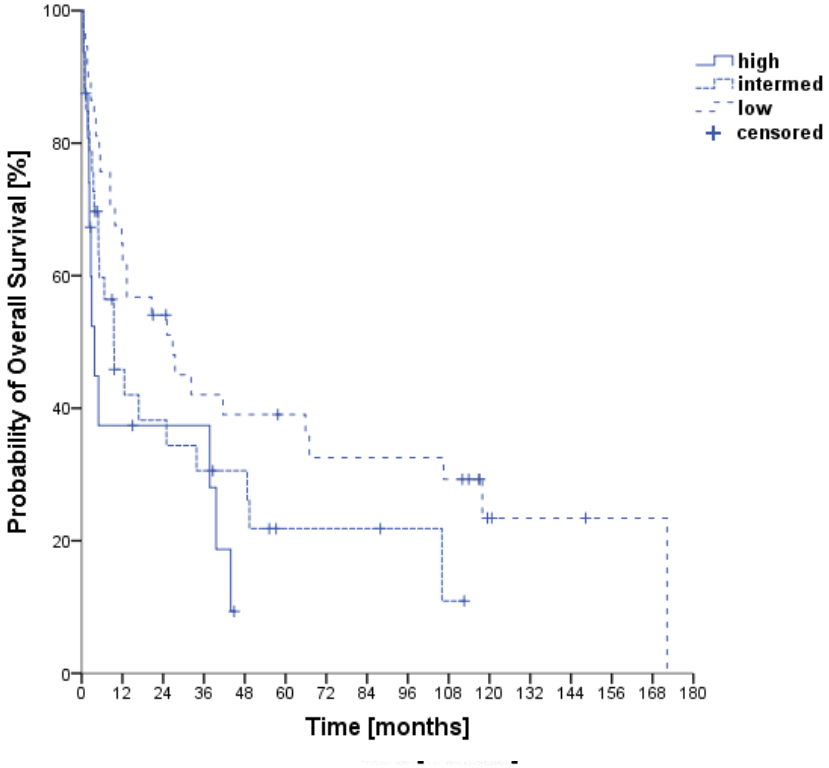


Figure 12. Overall survival for patients according to 3-F prognostic score.

Table 5. Survival according to MSKCC, IELSG and 3-F factor prognostic model

Prognostic score	Overall survival Median (95%CI)	*p* value	Progression-free survival Median (95%CI)	*p* value
MSKCC		0.012		0.17
1	67.0 months (0-154.3)		28.2 months (0-67.9)	
2	12.7 months (4.0-21.2)		6.5 months (0.26-12.7)	
3	3.8 months (1.5-6.1)		3.0 (1.9-4.6)	
IELSG[a]		0.039		0.22
0-1	41.6 months (8.9-74.3)		19.2 months (0-54.7)	
2-3	9.5 months (4.5-14.5)		3.8 (2.6-5.0)	
4	3.5 months (0.7-6.3)		3.3 (1.9-4.7)	
3-F prognostic model		0.048		0.28
Low	26.8 months (5.9-47.7)		11.4 months (0-25.6)	
Intermediate	9.5 months (2.3-16.7)		3.8 months (0-9.3)	
High	3.8 months (1.9-5.7)		3.0 months (1.4-4.6)	

Abbreviations: 95%CI: 95% confidence interval; MSKCC: Memorial Sloan Kettering Cancer Centre prognostic score [Abrey *et al.* 2006]; IELSG: International Extranodal Lymphoma Study Group prognostic score [Ferreri *et al.* 2003]; 3-F prognostic model: three-factor prognostic model [Jang *et al.* 2016].

[a]Maximal IELSG score was 4, due to missing data on cerebrospinal fluid protein level

Median OS of patients with low CCI (CCI=2), moderate CCI (CCI=3-4) and severe CCI (CCI≥5) was compared. Median OS of the patients with low, moderate and severe CCI were 9.8 months, 13.3 months and 32.2 months, respectively. No significant difference was reported (p=0.48).

3.7 Retrospective and prospective PCNSL studies identified by review

Altogether 13 retrospective PCNSL studies (1960 patients included) and 12 prospective PCNSL studies (694 patients included) were identified, published between January 2010 and November 2015. In general, prospective studies were conducted on a relative small number of patients (average 58 patients; range 8-66) with an exemption of G-PCNSL-SG-1 trial, which was conducted on 318 patients (per-protocol cohort). Median patient age within retrospective studies ranged from 54 years to 82 years, and within prospective studies between 42 years and 75 years. Detailed patient characteristics, including age and PS, are summarized in Appendix Table 1 and 2. Applied treatment regimens varied extensively. Overall, HD-MTX contained chemotherapy was the most applied protocol within prospective and retrospective studies. Monotherapy with HD-MTX was applied only in one retrospective study. WBRT was conducted in 33.3% of prospective studies and in 61.5% of retrospective studies. In many of prospective studies median OS has not been reached within the short observation period [Omuro *et al.* 2015a, Pulczynski *et al*. 2015, Wang *et al.* 2014]. Only few of them reported impaired OS, ranging from 17 months to 29 months [Thiel *et al.* 2010, Fritsch *et al.* 2011, Ferreri *et al.* 2009]. Median OS in retrospective studies varied from 9 months to 84 months [Cobert *et al.* 2010, Kellog *et al*. 2014]. Response rate and survival (OS, PFS) are shown in Appendix Table 1 and 2.

3.8 Early death in PCNSL patients

ED occurred in 24 patients (27.9%). Median age of these patients was 67.5 years. In the great majority of patients, poor PS (ECOG score 2-4: 75%) as well as moderate or severe CCI (CCI ≥3: 83.3%) were reported. Twelve patients received only one cycle of chemotherapy. Sepsis or severe infection was documented in 8 of these patients (66.7%). In four of the patients therapy was not continued due to PS deterioration. Progress was reported in 4 patients.

4 Discussion

The issue whether clinical results of cancer patients treated in controlled clinical trials and patients‘ outcome achieved within these trials resemble “real-life” findings has challenged researchers and practitioners for years. Possible bias could be caused by restrictive inclusion criteria within clinical trials (such as age restriction [61%], absence of comorbidities [83%], adequate kidney function [72%], adequate PS [70%], adequate liver function [69%], adequate life expectancy [20%]) [Bellera *et al.* 2013]) and by differences in care due to clinical trial participation (e.g. closer follow-up or more precise application of therapies). Few studies have showed that participation in clinical trial is associated with improved outcome per se [Braunholtz *et al.* 2001, Mol *et al.* 2013].

In 2014, Unger *et al.* conducted the largest study so far, comparing cancer patients treated within SWOG clinical trials (21 controlled trials, including 5,190 patients) and patients treated outside controlled studies selected from the SEER database (69,187 patients). It was found that trial patients were significantly younger in comparison to non-trial patients, whereby almost 20% more patients within SEER groups were aged ≥65 years comparing to trial patients. Improved OS was reported for patients treated within controlled trials. Interestingly, improved OS was only observed for the first year after diagnosis and was leveled out in the long-term follow-up. Improved short-term survival for trial patients was explained by the exclusion of sicker patients from clinical trials through eligibility criteria regarding to comorbidity and PS [Unger *et al.* 2014]. Patients with PCNSL were not included in this study.

This study presented here was conducted in order to evaluate whether these described findings are applicable to a PCNSL population.

Indeed, results of this study showed that PCNSL patients treated within the controlled clinical trial were significantly younger and fitter comparing to patients treated outside the G-PCNSL-SG-1 trial. Furthermore, more TRIAL patients had a low-risk PCNSL constellation according to all three available PCNSL prognostic scores compared to R-LIFE patients. Analyzing OS between the TRIAL and the R-LIFE group, no significant difference was seen at a statistical level (p=0.18). However, median OS in the TRIAL group was 33.8 months comparing to only 9.3 months in R-LIFE. Thus, the observed survival benefit of 2 years implies that there is a clinical important

difference regarding outcome between TRIAL and R-LIFE patients although the number of patients evaluated was not sufficient to prove this at a statistical level. In other words, since the HR was 0.67, the longer median survival of about 2 year for TRIAL patients could be translated in a survival benefit of 33%.

Median OS for all patients in the entire PCNSL cohort was only 13.3 months. This is markedly inferior in comparison to published data of controlled trial (Appendix Table 2). In many of controlled trials, median OS has not been reached [Omuro *et al.* 2015a, Pulczynski *et al.* 2015, Wang *et al.* 2014]. Kasenda *et al.* reported median OS of 104 months [Kasenda *et al.* 2012]. Yet, it should be mentioned, these trials were conducted on a highly selected population of patients, regarding alter and functional status [Kasenda *et al.* 2012, Omuro *et al.* 2015a]. On the other hand, Pulczynski *et al.* reported outcome in elderly patients (median age 64 years), however with a follow-up from 22 months only [Pulczynski *et al.* 2015]. A possible explanation for the poor outcome of our entire PCNSL cohort could be seen in the advanced age of the study population, considering that almost half of these patients were aged 70 years or older. Looking at the data obtained in other studies conducted in older patients, similar results are reported. A study involving 30 elderly PCNSL patients with a median age of 70 years reported comparable OS and PFS of 15.4 months and 5.9 months, respectively [Illerhaus *et al.* 2009]. Likewise, EORTC 26952 trial showed an OS of only 14.3 months in patients older than 60 years [Hoang-Xuan *et al.* 2003]. Looking separately survival data for patients above 70 years within the G-PCNSL-SG-1 trial similar data are obtained: median OS and PFS were 12.5 months and 4.0 months, respectively [Roth *et al.* 2012].

Although PCNSL is a disease affecting predominantly older patients [Villano *et al.* 2011], these patients are barely present in PCNSL controlled trials. The majority of prospective PCNSL trials reported data based on patients ≤60 years (Appendix Table 2). Under-representation of older patients with cancer in controlled trials is a well-known problem. The proportions of the patient populations enrolled in controlled trials aged ≥65, ≥70, and ≥75 years were 36%, 20%, and 9% compared with 60%, 46%, and 31%, respectively, in the general US cancer population [Talarico *et al.* 2004]. Just like that, in G-PCNSL-SG-1 trial only 21% of patients were 70 years or older [Roth *et al.* 2012]. Numerous studies exclude patients aged 65 years or older [Fritsch *et al.* 2011, Bellera *et al.* 2013, Kasenda *et al.* 2015a]. Median age in the entire cohort of this presented study was 68 years; yet, there was a significant difference in

proportion of patients older than 70 years among TRIAL und R-LIFE group, 15.0% *vs.* 53.4%, respectively.

Patients treated within controlled trials are not only younger, but also fitter (as shown in Appendix Table 1 and 2). This pattern was also observed within this study population, given that patients in TRIAL group were significant fitter with better PS. ECOG score 0-1 was observed in 80.0% of TRIAL patients comparing to only 38.4% patients in R-LIFE group. Good PS (resembling ECOG score ≤2) is often stated in inclusion criteria [Rubenstein *et al.* 2013a]. It is well known, that additionally to age, PS is the most reproducible prognostic factor [Ferreri *et al.* 2003, Batchelor *et al.* 2003, Haldorsen *et al.* 2004]. Karnofsky index ≥70% was associated with better OS and PFS at initial diagnosis of PCNSL as well as at relapse [Xie *et al.* 2015, Langner-Lemercier *et al.* 2016]. In a recently published meta-analysis in elderly PCNSL patients, Kasenda *et al.* demonstrated that Karnofsky index ≥70% was the strongest prognostic factor for mortality (p<0.001) [Kasenda *et al.* 2015b].

Comorbidities were also known to be predictor of mortality, whereby the CCI is the most widely used comorbidity index. Yet, in contrast to many hematologic malignancies and solid tumors [Ording *et al.* 2013, Saussele *et al.* 2015], in PCNSL, comorbidity was not shown to be associated with increased mortality [Puri *et al.* 2014]. In this analysis presented here, comorbidity was also not associated with increased mortality. Many of patients (50%) had moderate comorbidity (corresponding a CCI of 3-4). Thus, interestingly, despite frequent exclusion of patients with comorbidity from controlled trials, no difference was observed comparing comorbidities between TRIAL and R-LIFE group.

Taken altogether, our PCNSL patient population revealed a relatively poor prognosis. This was also confirmed applying PCNSL prognostic models in this patient population. According to all three available PCNSL prognostic models, the majority of patients had intermediate or poor prognosis (60-86% of all of patients, depending on prognostic model), which could additionally explain the poor outcome. Comparing distribution of patients in MSKCC score classes to original MSKCC population, 46% of class 3 patients *vs.* only 26% in MSKCC original population [Abrey *et al.* 2006] were identified. Rate of class 2 patients was consistent. Due to lack of CSF data a complete IELSG score had not been calculated, making a true comparison with the original IELSG population impossible. The proportion of high-risk patients in the 3-F

prognostic model population [Jang *et al.* 2016] was comparable to our patients. Nevertheless, it is to be mentioned that comparably less high-risk patients were observed in TRIAL group comparing to R-LIFE group (3-F prognostic score: p=0.001; MSKCC score: p=0.07, respectively) (Table 1). Recently, Jang *et al.* showed that all three prognostic scores are equally good in recognizing high-risk patients' groups, however 3-F prognostic model was significantly better at predicting 5-year OS of low-risk (3-F prognostic model *vs*. IELSG: p=0.002, 3-F prognostic model *vs*. MSKCC: p=0.003) [Jang *et al*. 2016]. In this analysis, the prognostic value of all three prognostic scores could have been valuated. Significant difference in OS was observed, regardless of applied prognostic score. MSKCC seems to be more potent comparing to other scores (the OS difference between risk groups was higher according to MSKCC classification (p=0.012), than according to IELSG and 3-F prognostic score (p=0.039 and p=0.048, respectively) (Table 5).

In the previously mentioned study from Unger *et al.,* it was pointed out that participation in a controlled trial was not associated with improved OS for good-prognosis diseases, but it was associated with better survival for poor-prognosis diseases – like PCNSL. Therefore reducing eligibility criteria could improve access to controlled trials for PCNSL patients with the potential chance of better outcome [Unger *et al.* 2014].

Due to analyzing data of a single-center study only, it could also be considered *per se* as a possible reason for inferior survival data (e.g. inadequate application of therapy, poor supportive therapy, etc.). However, comparing survival data from the TRIAL patients with the original G-PCNSL-SG-1 population, comparable results were observed. OS in the TRIAL group was 33.8 months comparing to 35.6 months in original G-PCNSL-SG-1 population. Reported PFS was also in both populations almost identical (PFS in TRIAL patients *vs.* G-PCNSL-SG-1 population was 25.1 months *vs.* 25.5 months) [Thiel *et al.* 2010]. Therefore, a bias due to this single-center can be excluded.

A possible additional explanation for the poor outcome observed in this patient population could also be seen in the therapy approach. HD-MTX monotherapy was applied in a majority of patients (84.6%) as it was considered as a standard at that

time [Thiel *et al.* 2010]. The activity of this approach is not satisfactory, given the fact that only 20% patients achieve long-term survival [Batchelor *et al.* 2003]. These data are about comparable with other published studies with HD-MTX alone. The NOA-03 trial reported a median OS of 25 months [Herrlinger *et al.* 2005]. Likewise, Gaviani *et al.* reported an OS of 20 months in a study of only 17 elderly patients treated with HD-MTX alone [Gaviani *et al.* 2016].

Although there is no well-defined standard treatment for patients with PCNSL, HD-MTX monotherapy is currently considered as a “minimal” therapy by many colleagues in this field [Korfel 2016] and meanwhile a polychemotherapy approach is advised. HD-MTX in combination with additional chemotherapy (Ara-C, thiotepa) and immunotherapy (rituximab) were shown to improve outcome [Wang *et al.* 2014, Kasenda *et al.* 2015a]. Ferreri *et al.* showed that addition of Ara-C leads to better response rates (CR 16% *vs.* 46%; *p*=0.06) [Ferreri *et al.* 2009]. Trials with rituximab reported excellent response rates, leading to CR in up to 100% patients [Birnbaum *et al.* 2012]. Furthermore, it was shown that addition of rituximab could improve not only ORR but OS as well [Holdhof *et al.* 2014]. In a study from Holdhoff *et al.*, median OS for patients that received R-HD-MTX was not reached comparing to only 16.3 months in HD-MTX group [Holdhof *et al.* 2014].

Given the known low long-term PFS, consolidation therapy could play an important role in PCNSL therapy. WBRT as consolidation therapy showed inadequate efficacy and was associated with severe neurotoxicity [Thiel *et al.* 2010]. Based on these report, WBRT was omitted in this analysis in first-line therapy. However, alternative consolidation strategies, like non-cross-resistant polychemotherapy or HDC with ASCT were here also not included. A few phase II studies with HDC and ASCT strategy showed encouraging outcomes with superior survival rates. In study conducted by Omuro *et al.*, 2-year PFS and OS were 81% [Omuro *et al.* 2015a]. Miayo *et al.* reported a 3-year OS of 81% in patients undergoing ASCT [Miyao *et al.* 2014]. A retrospective study by Madle *et al.* confirmed positive impact of HDC and ASCT regarding survival (3-year OS in patients with ASCT comparing to non-ASCT was 85.2% *vs*. 35.2%) and observed ASCT as an independent prognostic factor in a multivariate analysis [Madle *et al.* 2015]. This consolidation strategy seems to be highly effective, yet the generalizability of this approach is questionable. It is primarily addressed to young (aged <65 years) and fit patients, thereby not mirroring the

reality of PCNSL patients as mentioned above. Application of intensive protocols and findings obtained within controlled trials to non-comparable patient populations may result in patient harm.

Short median OS reported in this study may well be due to a high proportion of patients dying within 120 days from histological diagnosis. ED was reported in almost one third of the patients. These rates are noticeably higher comparing to ED in nodal NHL (7%) [Bairey *et al.* 2013]. ED rates regarding PCNSL were so far not reported. Patients with poor PS and moderate or severe comorbidity were at a higher risk of ED. The main issue in these patients was not disease progress, but high toxicity burden. One half of the ED patients developed severe infections or deterioration of PS, which made therapy continuation not possible.

Having the actual treatment strategies in mind, it seems that a part of the patients analyzed in this study had been undertreated with HD-MTX monotherapy. Younger and fitter patients would have probably benefited from HDC with ASCT. On the other hand, a group of patients that died due to treatment-related mortality were obviously over-treated.

An interesting concept for elderly patients (≥60 years) was recently presented in a study conducted by the ANOCEF-GOELAMS intergroup. Patients were stratified according to PS (Karnofsky index <60% *vs.* ≥60%) to HD-MTX with only one additional agent (temozolomide) or to a more intensive polychemotherapy (HD-MTX, procarbazine, vincristine, and Ara-C), respectively [Omuro *et al.* 2015b]. Median OS was 31 months in the polychemotherapy group and 14 months in the HD-MTX/temozolomide group. No differences were noted in toxic effects between the two groups. Survival data observed in elderly, unfit patient group (HD-MTX/temozolomide group) were about comparable to survival data in this study presented here. However, this patient stratification offers a good selection of patients that are eligible for more intensive chemotherapy protocols.

A possible alternative for elderly and frail patients could also be seen in new drugs targeting signaling and immune-checkpoint pathways as well as in immunomodulatory drugs. In a recently conducted phase I study, lenalidomide was shown to have positive impact in relapsed/refractory PCNSL [Rubenstein *et al.* 2016]. In 8 from 13 heavily pretreated PCNSL patients, lenalidomide maintenance therapy

(following local radiation or R-MTX salvage therapy) induced at least PR. The role of the Bruton-tyrosinkinase inhibitor ibrutinib (ClinicalTrials.gov number NCT02315326) as well as the PD-1 inhibitor pembrolizumab (ClinicalTrials.gov number NCT02779101) is also currently being investigated in PCNSL.

An additional explanation for the poor outcome in this study could be seen in a long follow-up of almost 10 years. The majority of published studies report on patients with an average follow-up of 3 years or less [Ferreri *et al.* 2009, Wang *et al.* 2014]. As a result, OS and PFS are often overestimated, while risk of relapse and treatment related toxicity are too often underestimated. Furthermore, interpretation of the results of a trial is always problematic when the proportion of missing events is substantial. Event rate in G-PCNSL-SG-1 trial was about 50% [Thiel *et al.* 2010], whereas other trials reported an event rate of only about 20% [Omuro *et al.* 2015a]. In this study, the “pro-active” follow-up resulted in a greater number of events (70%) thereby leading to poorer outcome (median OS in “pro-active” follow-up patients and standard follow-up were 25.0 months and 39.6 months, respectively) (Table 4). This underlies the importance of an active and long-term patient follow-up as well as the importance of update of survival and relapse data. In this manner we could obtain more accurate and valid “real-life” data that are needed for reliable treatment guidelines.

To the best of our knowledge, data comparing “real-life” outcome with outcome in controlled trials concerning PCNSL patients has not been generated and published so far. The data presented here are based on a long follow-up of about 10 years. Furthermore, for many patients a complete follow-up was available − considering a high event rate with “real-life” survival data in this study. However, there are some limitations to this study: the single-center setting, retrospective design, and a small study population (73 patients compared with 20 patients only).

Taken together, this study shows that survival of PCNSL patients treated outside a controlled trial, but analogues to the G-PCNSL-SG-1 trial was poor. The treatment and management of patients with PCNSL clearly requires improvement. Recently published multi-center trials using HDC with ASCT as a part of first-line treatment showed improved survival rates. Yet, they were associated with high treatment-

related burden, whereas data regarding neurotoxicity were not reported at all. Furthermore, these regimens are restricted solely to young patients, who present the minority of PCNSL patients. Young and fit patients are usually overrepresented in clinical trials. In the future, a careful review of trial eligibility criteria is required in order to define the actual patient population, tailor appropriately therapy regimens and provide better and individualized clinical care.

5 Summary

Treatment of patients with PCNSL presents still a challenge. Recently published studies showed encouraging results. At the same time, outcome in “real-life” settings appears to be less favorable. This study was conducted in order to compare the patients’ characteristics and clinical outcome of patients treated within the multi-center German Primary CNS Lymphoma Study Group 1 trial (TRIAL) and patients treated outside this trial (R-LIFE). Altogether, 93 patients were analyzed, 20 patients from that were treated within the controlled trial.

The main results of the study are:

1. Patients treated within the controlled clinical trial were younger, fitter and had fewer a poor-risk disease comparing to patients treated outside the controlled trial.
2. Patients treated within the TRIAL group had a better outcome comparing to R-LIFE patients, yet that appeared not to be statistically significant, but, however, clinically relevant, since the difference in OS was 2 years.

Other important findings are:

1. Survival of patients treated in this study was inferior comparing to survival data in other published PCNSL studies.
2. “Pro-active” follow-up have a negative influence on survival data in PCNSL patients.
3. All three available prognostic scores for PCNSL have been shown to stratify patients into groups with significantly different prognosis regarding OS.
4. Patients with impaired performance status and moderate or severe comorbidity were at a higher risk of ED.

6 List of Figures

7 List of Tables

8 References

1. Abrey LE, DeAngelis LM, Yahalom J: Long-term survival in primary CNS lymphoma. J Clin Oncol. 16. 859-863 (1998)

2. Abrey LE, Moskowitz CH, Mason WP, Crump M, Stewart D, Forsyth P, Paleologos N, Correa DD, Anderson ND, Caron D, Zelenetz A, Nimer SD, DeAngelis LM: Intensive methotrexate and cytarabine followed by high-dose chemotherapy with autologous stem-cell rescue in patients with newly diagnosed primary CNS lymphoma: an intent-to-treat analysis. J Clin Oncol. 21. 4151-4156 (2003)

3. Abrey LE, Batchelor TT, Ferreri AJ, Gospodarowicz M, Pulczynski EJ, Zucca E, Smith JR, Korfel A, Soussain C, DeAngelis LM, Neuwelt EA, O'Neill BP, Thiel E, Shenkier T, Graus F, van den Bent M, Seymour JF, Poortmans P, Armitage JO, Cavalli F; International Primary CNS Lymphoma Collaborative Group: Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol. 23. 5034-5043 (2005)

4. Abrey LE, Ben-Porat L, Panageas KS, Yahalom J, Berkey B, Curran W, Schultz C, Leibel S, Nelson D, Mehta M, DeAngelis LM: Primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center prognostic model. J Clin Oncol. 24. 5711-5715 (2006)

5. Bairey O1, Bar-Natan M, Shpilberg O. Early death in patients diagnosed with non-Hodgkin's lymphoma. Ann Hematol. 92. 345-50 (2013)

6. Bataille B, Delwail V, Menet E, Vandermarcq P, Ingrand P, Wager M, Guy G, Lapierre F: Primary intracerebral malignant lymphoma: report of 248 cases. J Neurosurg. 92. 261-266 (2000)

7. Batchelor T, Carson K, O'Neill A, Grossman SA, Alavi J, New P, Hochberg F, Priet R: Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. J Clin Oncol. 21. 1044-1049 (2003)

8. Bellera C, Praud D, Petit-Monéger A, McKelvie-Sebileau P, Soubeyran P, Mathoulin-Pélissier S: Barriers to inclusion of older adults in randomised controlled clinical trials on Non-Hodgkin's lymphoma: a systematic review. Cancer Treat Rev. 39. 812-817 (2013)

9. Bellinzona M, Roser F, Ostertag H, Gaab RM, Saini M: Surgical removal of primary central nervous system lymphomas (PCNSL) presenting as space occupying lesions: a series of 33 cases. Eur J Surg Oncol. 31. 100-105 (2005)

10. Birnbaum T, Stadler EA, von Baumgarten L, Straube A: Rituximab significantly improves complete response rate in patients with primary CNS lymphoma. J Neurooncol. 109. 285-291 (2012)

11. Braunholtz DA, Edwards SJ, Lilford RJ: Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". J Clin Epidemiol. 54. 217-224 (2001)

12. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES: The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood. 117. 5019-5032 (2011)

13. Chamberlain MC, Johnston SK: High-dose methotrexate and rituximab with deferred radiotherapy for newly diagnosed primary B-cell CNS lymphoma. Neuro Oncol. 12. 736-744 (2010)

14. Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 40. 373-383 (1987)

15. Cobert J, Hochberg E, Woldenberg N, Hochberg F: Monotherapy with methotrexate for primary central nervous lymphoma has single agent activity in the absence of radiotherapy: a single institution cohort. J Neurooncol. 98. 385-393 (2010)

16. DeAngelis LM, Seiferheld W, Schold SC, Fisher B, Schultz C: Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93–10. J Clin Oncol. 20. 4643-4648 (2002)

17. Dolecek TA, Propp JM, Stroup NE, Kruchko C: CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. Neuro-oncol. 14 (Suppl 5): v1-v49 (2012)

18. Ferreri AJ, Blay JY, Reni M, Pasini F, Spina M, Ambrosetti A, Calderoni A, Rossi A, Vavassori V, Conconi A, Devizzi L, Berger F, Ponzoni M, Borisch B, Tinguely M, Cerati M, Milani M, Orvieto E, Sanchez J, Chevreau C, Dell'Oro S, Zucca E, Cavalli F: Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. J Clin Oncol. 21. 266-272 (2003)

19. Ferreri AJM, Reni M, Foppoli M, Martelli M, Pangalis GA, Frezzato M, Cabras MG, Fabbri A, Corazzelli G, Ilariucci F, Rossi G, Soffietti R, Stelitano C, Vallisa D, Zaja F, Zoppegno L, Aondio GM, Avvisati G, Balzarotti M, Brandes AA, Fajardo J, Gomez H, Guarini A, Pinotti G, Rigacci L, Uhlmann C, Picozzi P, Vezzulli P, Ponzoni M, Zucca E, Caligaris-Cappio F, Cavalli F: High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. Lancet. 374. 1512-1520 (2009)

20. Fritsch K, Kasenda B, Hader C, Nikkhah G, Prinz M, Haug V, Haug S, Ihorst G, Finke J, Illerhaus G: Immunochemotherapy with rituximab, methotrexate, procarbazine, and lomustine for primary CNS lymphoma (PCNSL) in the elderly. Ann Oncol. 22. 2080-2085 (2011)

21. Gaviani P, Simonetti G, Innocenti A, Lamperti E, Botturi A, Silvani A: Safety and efficacy of primary central nervous system lymphoma treatment in elderly population. Neurol Sci. 37. 131-133 (2016)

22. Gavrilovic IT, Hormigo A, Yahalom J, DeAngelis L.M, Abrey LE: Long-term follow-up of high-dose methotrexate-based therapy with and without whole brain irradiation for newly diagnosed primary CNS lymphoma. J Clin Oncol. 24. 4570-4574 (2006)

23. Gerstner ER, Abrey LE, Schiff D, Ferreri AJ, Lister A, Montoto S, Tsang R, Thiel E, Graus F, Behringer D, Illerhaus G, Weaver S, Wen P, Voloschin A, Harris NL, Batchelor TT: CNS Hodgkin lymphoma. Blood. 112. 1658-1661(2008)

24. Ghesquières H, Drouet Y, Sunyach MP, Sebban C, Chassagne-Clement C, Jouanneau E, Honnorat J, Biron P, Blay JY: Evidence of time-dependent prognostic factors predicting early death but not long-term outcome in primary CNS lymphoma: a study of 91 patients. Hematol Oncol. 31. 57-64 (2013)

25. Guha-Thakurta N, Damek D, Pollack C, Hochberg FH: Intravenous methotrexate as initial treatment for primary central nervous system lymphoma: response to therapy and quality of life of patients. J Neurooncol. 43. 259-268 (1999)

26. Haldorsen IS, Aarseth JH, Hollender A, Larsen JL, Espeland A, Mella O: Incidence, clinical features, treatment and outcome of primary central nervous system lymphoma in Norway. Acta Oncol. 43. 520-529 (2004)

27. Herrlinger U, Uhl M, Blaicher HP, Karnath HO, Kanz L, Bamberg M, Weller M: NOA-03 trial of high-dose methotrexate in primary central nervous system lymphoma: final report. Ann Neurol. 57. 843-847 (2005)

28. Hoang-Xuan K, Taillandier L, Chinot O, Soubeyran P, Bogdhan U, Hildebrand J, Frenay M, De Beule N, Delattre JY, Baron B; European Organization for Research and Treatment of Cancer Brain Tumor Group: Chemotherapy alone as initial treatment for primary CNS lymphoma in patients older than 60 years: a multicenter phase II study (26952) of the European Organization for Research and Treatment of Cancer Brain Tumor Group. J Clin Oncol. 21. 2726-2731 (2003)

29. Holdhoff M, Ambady P, Abdelaziz A, Sarai G, Bonekamp D, Blakeley J, Grossman SA, Ye X: High-dose methotrexate with or without rituximab in newly diagnosed primary CNS lymphoma. Neurology. 83. 235-239 (2014)

30. Illerhaus G, Marks R, Müller F, Ihorst G, Feuerhake F, Deckert M, Ostertag C, Finke J: High-dose methotrexate combined with procarbazine and CCNU for primary CNS lymphoma in the elderly: results of a prospective pilot and phase II study. Ann Oncol. 20. 319-325 (2009)

31. Iwabuchi M, Shibamoto Y, Sugie C, Ayakawa S, Ogino H, Baba F: Partial-brain radiotherapy for primary central nervous system lymphoma: multi-institutional experience. J Radiat Res. 57. 164-168 (2016)

32. Jang JE, Kim YR, Kim SJ, Cho H, Chung H, Lee JY, Park H, Kim Y, Cheong JW, Min YH, Kim JS: A new prognostic model using absolute lymphocyte count in patients with primary central nervous system lymphoma. Eur J Cancer. 57. 127-135 (2016)

33. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc. 53. 457-481 (1958)

34. Kasenda B, Schorb E, Fritsch K, Finke J, Illerhaus G: Prognosis after high-dose chemotherapy followed by autologous stem-cell transplantation as first-line treatment in primary CNS lymphoma - a long-term follow-up study. Ann Oncol. 23. 2670-2675 (2012)

35. Kasenda B, Schorb E, Fritsch K, Finke J, Illerhaus G: Prognosis after high-dose chemotherapy followed by autologous stem-cell transplantation as first-line treatment in primary CNS lymphoma--a long-term follow-up study. Ann Oncol. 26. 608-611 (2015a)

36. Kasenda B, Ferreri AJ, Marturano E, Forst D, Bromberg J, Ghesquieres H, Ferlay C, Blay JY, Hoang-Xuan K, Pulczynski EJ, Fosså A, Okoshi Y, Chiba S, Fritsch K, Omuro A, O'Neill BP, Bairey O, Schandelmaier S, Gloy V, Bhatnagar N, Haug S, Rahner S, Batchelor TT, Illerhaus G, Briel M: First-line treatment and outcome of elderly patients with primary central nervous sys- tem lymphoma (PCNSL)-a systematic review and individual patient data meta-analysis. Ann Oncol 26. 1305-1313 (2015b)

37. Kellogg RG, Straus DC, Karmali R, Munoz LF, Byrne RW: Impact of therapeutic regimen and clinical presentation on overall survival in CNS lymphoma. Acta Neurochir (Wien). 156. 355-365 (2014)

38. Kim YR, Kim SH, Chang JH, Suh CO, Kim SJ, Kim Y, Hwang DY, Jang JE, Hyun SY, Cheong JW, Min YH, Kim JS: Early response to high-dose methotrexate, vincristine, and procarbazine chemotherapy-adapted strategy for primary CNS lymphoma: no consolidation therapy for patients achieving early complete response. Ann Hematol. 93. 211-209 (2014)

39. Korfel A, Thiel E, Martus P, Möhle R, Griesinger F, Rauch M, Röth A, Hertenstein B, Fischer T, Hundsberger T, Mergenthaler HG, Junghanß C, Birnbaum T, Fischer L, Jahnke K, Herrlinger U, Roth P, Bamberg M, Pietsch T, Weller M: Randomized phase III study of whole-brain radiotherapy for primary CNS lymphoma. Neurology. 84. 1242-1248 (2015)

40. Korfel A: Standardtherapie für jüngere Patienten? Info Onkol. 19. 14-16 (2016)

41. Langner-Lemercier S, Houillier C, Soussain C, Ghesquières H, Chinot O, Taillandier L, Soubeyran P, Lamy T, Morschhauser F, Benouaich-Amiel A, Ahle G, Moles-Moreau MP, Moluçon-Chabrot C, Bourquard P, Damaj G, Jardin F, Larrieu D, Gyan E, Gressin R, Jaccard A, Choquet S, Brion A, Casasnovas O, Colin P, Reman O, Tempescul A, Marolleau JP, Fabbro M, Naudet F, Hoang-Xuan K, Houot R: Primary CNS lymphoma at first relapse/progression:

characteristics, management, and outcome of 256 patients from the French LOC network. Neuro Oncol. 18. 1297-303 (2016)

42. Levy O, DeAngelis LM, Filippa DA, Panageas KS, Abrey LE: Bcl-6 predicts improved prognosis in primary central nervous system lymphoma. Cancer. 112. 151-156 (2008)

43. Ly KI, Crew LL, Graham CA, Mrugala MM: Primary central nervous system lymphoma treated with high-dose methotrexate and rituximab: A single-institution experience. Oncol Lett. 11. 3471-3476 (2016)

44. Madle M, Krämer I, Lehners N, Schwarzbich M, Wuchter P, Herfarth K, Egerer G, Ho AD, Witzens-Harig M: The influence of rituximab, high-dose therapy followed by autologous stem cell transplantation, and age in patients with primary CNS lymphoma. Ann Hematol. 94. 1853-1857 (2015)

45. Mitchell AP, Harrison MR, George DJ, Abernethy AP, Walker MS, Hirsch BR: Clinical trial subjects compared to "real world" patients: Generalizability of renal cell carcinoma trials. J Clin Oncol. 32. suppl; abstr 6510 (2014)

46. Miyao K, Sakemura R, Imai K, Sakai T, Tsushita N, Kato T, Niimi K, Ono Y, Sawa M: Upfront autologous stem-cell transplantation with melphalan, cyclophosphamide, etoposide, and dexamethasone (LEED) in patients with newly diagnosed primary central nervous system lymphoma. Int J Hematol. 100. 152-158 (2014)

47. Mol L, Koopman M, van Gils CWM, Ottevanger PB, Punt CJA: Comparison of treatment outcome in metastatic colorectal cancer patients included in a clinical trial versus daily practice in The Netherlands. Acta Oncol. 52. 950-955 (2013)

48. Morris PG, Correa DD, Yahalom J, Raizer JJ, Schiff D, Grant B, Grimm S, Lai RK, Reiner AS, Panageas K, Karimi S, Curry R, Shah G, Abrey LE, DeAngelis LM, Omuro A: Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. J Clin Oncol. 31. 3971-3979 (2013)

49. National Comprehensive Cancer Network. Central Nervous System Cancers (Version 1.2016). https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed May 20, 2017.

50. Nelson DF: Radiotherapy in the treatment of primary central nervous system lymphoma (PCNSL). J Neurooncol. 43. 241-247 (1999)

51. Omuro A, Correa DD, DeAngelis LM, Moskowitz CH, Matasar MJ, Kaley TJ, Gavrilovic IT, Nolan C, Pentsova E, Grommes CC, Panageas KS, Baser RE, Faivre G, Abrey LE, Sauter CS: R-MPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma. Blood. 125. 1403-1410 (2015a)

52. Omuro A, Chinot O, Taillandier L, Ghesquieres H, Soussain C, Delwail V, Lamy T, Gressin R, Choquet S, Soubeyran P, Huchet A, Benouaich-Amiel A, Lebouvier-Sadot S, Gyan E, Touitou V, Barrié M, del Rio MS, Gonzalez-Aguilar A, Houillier C, Delgadillo D, Lacomblez L, Tanguy ML, Hoang-Xuan K: Methotrexate and temozolomide versus methotrexate, procarbazine, vincristine, and cytarabine for primary CNS lymphoma in an elderly population: an intergroup ANOCEF-GOELAMS randomised phase 2 trial. Lancet Haematol. 2. e251-e259 (2015b)

53. Ording AG, Garne JP, Nyström PM, Frøslev T, Sørensen HT, Lash TL: Comorbid diseases interact with breast cancer to affect mortality in the first year after diagnosis-a Danish nationwide matched cohort study. PLoS ONE. 8(10):e76013 (2013)

54. Phillips EH, Fox CP, Cwynarski K: Primary CNS lymphoma. Curr Hematol Malig Rep. 9. 243-253 (2014)

55. Ponzoni M, Issa S, Batchelor TT, Rubenstein JL: Beyond high-dose methotrexate and brain radiotherapy: novel targets and agents for primary CNS lymphoma. Ann Oncol. 25. 316-322 (2014)

56. Pulczynski EJ, Kuittinen O, Erlanson M, Hagberg H, Fosså A, Eriksson M, Nordstrøm M, Østenstad B, Fluge Ø, Leppä S, Fiirgaard B, Bersvendsen H, Fagerli UM: Successful change of treatment strategy in elderly patients with primary central nervous system lymphoma by de-escalating induction and introducing temozolomide maintenance: results from a phase II study by the Nordic Lymphoma Group. Haematologica. 100. 534-540 (2015)

57. Puri S, Mehta T, Mehta K, Sheth K, Soni R, Joshi J, Vredenburgh JJ: Predictors of in-hospital mortality in patients with primary central nervous system lymphoma. Blood. 124. suppl; abstr 1699 (2014)

58. Roth P, Martus P, Kiewe P, Möhle R, Klasen H, Rauch M, Röth A, Kaun S, Thiel E, Korfel A, Weller M: Outcome of elderly patients with primary CNS lymphoma in the G-PCNSL-SG-1 trial. Neurology. 79. 890–896 (2012)

59. Rubenstein JL, Hsi ED, Johnson JL, Jung SH, Nakashima MO, Grant B, Cheson BD, Kaplan LD: Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). J Clin Oncol. 31. 3061-3068 (2013a)

60. Rubenstein JL, Gupta NK, Mannis GN, Lamarre AK, Treseler P: How I treat CNS lymphomas. Blood. 122. 2318-2330 (2013b)

61. Rubenstein JL, Fraser E, Formaker P, Lee JC, Chen N, Kock M, Cheung W, Wang X, Munster PN, Damato B: Phase I investigation of lenalidomide plus rituximab and outcomes of lenalidomide maintenance in recurrent CNS lymphoma. J Clin Oncol. 34. suppl; abstr 7502 (2016)

62. Saussele S, Krauss MP, Hehlmann R, Lauseker M, Proetel U, Kalmanti L, Hanfstein B, Fabarius A, Kraemer D, Berdel WE, Bentz M, Staib P, de Wit M,

Wernli M, Zettl F, Hebart HF, Hahn M, Heymanns J, Schmidt-Wolf I, Schmitz N, Eckart MJ, Gassmann W, Bartholomäus A, Pezzutto A, Leibundgut EO, Heim D, Krause SW, Burchert A, Hofmann WK, Hasford J, Hochhaus A, Pfirrmann M, Müller MC; Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung and the German CML Study Group: Impact of comorbidities on overall survival in patients with chronic myeloid leukemia: results of the randomized CML study IV. Blood. 126:42-49 (2015)

63. Schabet M: Epidemiology of primary CNS lymphoma. J Neurooncol. 43. 199-201 (1999)

64. Schalk E, Zeremski V, Fischer T: Impact of lymphopenia on prognosis of patients with primary central nervous system lymphoma. Eur J Cancer. 75. 280-283 (2017)

65. Schorb E, Kasenda B, Atta J, Kaun S, Morgner A, Hess G, Elter T, von Bubnoff N, Dreyling M, Ringhoffer M, Krause SW, Derigs G, Klimm B, Niemann D, Fritsch K, Finke J, Illerhaus G: Prognosis of patients with primary central nervous system lymphoma after high-dose chemotherapy followed by autologous stem cell transplantation. Haematologica. 98. 765-770 (2013)

66. Scordo, Bhatt V, Hsu M, Omuro AM, Matasar MJ, DeAngelis, Moskowitz CH, Giralt SA, Sauter CS: A comprehensive assessment of toxicities in patients with central nervous system lymphoma undergoing autologous stem cell transplantation using thiotepa, busulfan, and cyclophosphamide conditioning. Biol Blood Marrow Transplant. 23. 38-43 (2017)

67. Shah GD, Yahalom J, Correa DD, Lai RK, Raizer JJ, Schiff D, LaRocca R, Grant B, DeAngelis LM, Abrey LE: Combined immunochemotherapy with reduced whole-brain radiotherapy for newly diagnosed primary CNS lymphoma. J Clin Oncol 25. 4730-4735 (2007)

68. Shibamoto Y, Hayabuchi N, Hiratsuka J, Tokumaru S, Shirato H, Sougawa M, Oya N, Uematsu Y, Hiraoka M: Is whole-brain irradiation necessary for primary central nervous system lymphoma? Patterns of recurrence after partial-brain irradiation. Cancer. 97. 128-133 (2003)

69. Shiels MS, Pfeiffer RM, Hall HI, Li J, Goedert JJ, Morton LM, Hartge P, Engels EA: Proportions of Kaposi sarcoma, selected non-Hodgkin lymphomas, and cervical cancer in the United States occurring in persons with AIDS, 1980-2007. JAMA. 305.1450-1449 (2011)

70. Shiels, MS, Pfeiffer RM, Besson C, Clarke CA, Morton LM, Nogueira, L, Pawlish K, Yani EL, Suneja, G, Engels EA: Trends in primary central nervous system lymphoma incidence and survival in the U.S. Br J Haematol. 174. 417-424 (2016)

71. Shuster JJ: Median follow-up in clinical trials. J Clin Oncol. 9. 191-192 (1991)

72. Talarico L, Chen G, Pazdur R: Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. J Clin Oncol. 22. 4626-4631 (2004)

73. Thiel E, Korfel A, Martus P, Kanz L, Griesinger F, Rauch M, Röth A, Hertenstein B, von Toll T, Hundsberger T, Mergenthaler HG, Leithäuser M, Birnbaum T, Fischer L, Jahnke K, Herrlinger U, Plasswilm L, Nägele T, Pietsch T, Bamberg M, Weller M: High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. Lancet Oncol. 11. 1036-1047 (2010)

74. Unger JM, Barlow WE, Martin DP, Ramsey SD, LeBlanc M, Etzioni R, Hershman DL: Comparison of survival outcomes among cancer patients treated in and out of clinical trials. J Natl Cancer Inst. 106. dju002 (2014)

75. Villano JL, Koshy M, Shaikh H, Dolecek TA, McCarthy BJ: Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. Br J Cancer. 105. 1414-1418 (2011)

76. Wang HI, Aas E, Roman E, Howell D, Painter D, Smith A: Differences in medical cost and survival between trial and non-trial patients with acute myeloid leukaemia - a UK population-based propensity analysis. Value Health. 16. A323-A736 (2015)

77. Wang XX, Huang HQ, Bai B, Cai QQ, Cai QC, Gao Y, Xia YF, Xia ZJ, Jiang WQ: Clinical outcomes of patients with newly diagnosed primary central nervous system lymphoma are comparable on treatment with high-dose methotrexate plus temozolomide and with high-dose methotrexate plus cytarabine: a single-institution experience. Leuk Lymphoma. 55. 2497-2501 (2014)

78. Welch MR, Omuro A, Deangelis LM: Outcomes of the oldest patients with primary CNS lymphoma treated at Memorial Sloan-Kettering Cancer Center. Neuro Oncol. 14. 1304-1311 (2012)

79. Weller M, Martus P, Roth P, Thiel E, Korfel A: Surgery for primary CNS lymphoma? Challenging a paradigm. Neuro-Oncol. 14. 1481-1484 (2012)

80. Wieduwilt MJ, Valles F, Issa S, Behler CM, Hwang J, McDermott M, Treseler P, O'Brien J, Shuman MA, Cha S, Damon LE, Rubenstein JL: Immunochemotherapy with intensive consolidation for primary CNS lymphoma: a pilot study and prognostic assessment by diffusion-weighted MRI. Clin Cancer Res. 18. 1146-1155 (2012)

81. World Medical Association: World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 310. 2191-2194 (2013)

82. Xie H, Ahluwalia MS, Peereboom DM: The Cleveland Clinic experience with primary central nervous system lymphoma. Am J Clin Oncol. 38. 140-146 (2015)

83. Yanai H, Negishi H, Taniguchi T. The IRF family of transcription factors. Inception, impact and implications in oncogenesis. Oncoimmunology. 1. 1376–1386 (2012)

84. Zhu JJ, Gerstner ER, Engler DA, Mrugala MM, Nugent W, Nierenberg K, Hochberg FH, Betensky RA, Batchelor TT: High-dose methotrexate for elderly patients with primary CNS lymphoma. Neuro Oncol. 11. 211-215 (2009)

9 Danksagung

Ich danke meinem Chef und Lehrer, Herrn Prof. Dr. med. Thomas Fischer, für die Vergabe des Themas, für die Unterstützung und für die finale Revision der Arbeit.

Besonderer Dank gilt Herrn Dr. med. Enrico Schalk für die Betreuung und für die ständige Begleitung meiner Arbeit. Seine Anregungen und kritischen Kommentare haben zum guten Gelingen beigetragen.

Nicht zuletzt möchte ich mich bei Herrn Prof. Dr. med. Aleksandar Savić Universität Novi Sad, Serbien, bedanken, dass er mich als mein erster Lehrer für die Hämatologie begeistern konnte. Durch ihn erhielt ich Einblicke in die klinische Forschung und Wissenschaft, was eine wichtige Grundlage für die Arbeit an meiner Dissertation war.

12 Ehrenerklärung

Ich erkläre, dass ich die der Medizinischen Fakultät der Otto-von-Guericke-Universität zur Promotion eingereichte Dissertation mit dem Titel

Comparison of clinical outcome in PCNSL patients treated in and outside of clinical trial

(Vergleich der klinischen Ergebnisse von Patienten mit primärem ZNS-Lymphom, die innerhalb und außerhalb einer klinischen Studie behandelt wurden)

in der Klinik für Hämatologie und Onkologie der Medizinischen Fakultät der Otto-von-Guericke-Universität Magdeburg mit Unterstützung durch Prof. Dr. med. Thomas Fischer ohne sonstige Hilfe durchgeführt und bei der Abfassung der Dissertation keine anderen als die dort aufgeführten Hilfsmittel benutzt habe.

Bei der Abfassung der Dissertation sind Rechte Dritter nicht verletzt worden.

Ich habe diese Dissertation bisher an keiner in- oder ausländischen Hochschule zur Promotion eingereicht. Ich übertrage der Medizinischen Fakultät das Recht, weitere Kopien meiner Dissertation herzustellen und zu vertreiben.

Magdeburg, den 27.11.2017

Vanja Zeremski

10 Publikationen im Rahmen der Dissertation

1. Vollpublikation

   - **Zeremski V**, Koehler M, Fischer T, Schalk E: Characteristics and outcome of patients with primary CNS lymphoma in a "real-life" setting compared to a clinical trial. Ann Hematol. 95. 793-799 (2016)

   - Schalk E, **Zeremski V**, Fischer T: Impact of lymphopenia on prognosis of patients with primary central nervous system lymphoma. Eur J Cancer. 75. 280-283 (2017)

2. Abstracts

   - **Zeremski V**, Koehler M, Fischer T, Schalk E. A “pro-active” follow-up with higher completeness can significantly influence survival data. Oncol Res Treat. 38 (Suppl 5); abstract 508 (2015)

   - **Zeremski V**, Fischer T, Schalk E. Clinical outcome of primary CNS lymphoma comparing the setting of “real-life” with a clinical trial: A single centre experience of 95 patients. Oncol Res Treat. 38 (Suppl 5); abstract 707 (2015)

   - **Zeremski V**, Fischer T, Schalk E. Early death in patients with primary CNS lymphoma. Oncol Res Treat. 40 (Suppl 3); abstract 281 (2017)

3. Poster

   - **Zeremski V**, Köhler M, Fischer T, Schalk E. Eine „pro-aktive“ Nachbeobachtung mit höherer Vollständigkeit kann Überlebensdaten signifikant beeinflussen. Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Medizinische Onkologie 2015, 09.10.-13.10.2015, Basel/CH

   - **Zeremski V**, Fischer T, Schalk E. Early death in patients with primary CNS lymphoma. Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Medizinische Onkologie 2017, 29.09.-03.10.2017, Stuttgart

   - **Zeremski V**, Fischer T, Schalk E. Comparison of Clinical Features and Outcomes in Patients with Primary Central Nervous System Lymphoma Treated within and outside a Clinical Trial: a Retrospective Study. 59th American Society of Hematology Annual Meeting and Exposition 2017, 09. - 12.12.2017, Atlanta, GA, USA

4. Vorträge

   - **Zeremski V**, Fischer T, Schalk E. Vergleich klinischer Ergebnisse von Patienten mit primärem ZNS-Lymphom – therapiert außerhalb bzw. innerhalb

einer klinischen Studie. Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Medizinische Onkologie 2015; 09.10.-13.10.2015, Basel/CH

- Schalk E, **Zeremski V**, Fischer. Einfluss einer initialen Therapieverzögerung auf die Prognose bei Patienten mit primärem ZNS-Lymphom (PCNSL). Der 7. Sachsen-Anhaltische Krebskongress, 10.03.-11.03.2017, Halle/Saale

11 Darstellung des Bildungsweges

Der Lebenslauf ist in der Online-Version aus Datenschutzgründen nicht enthalten.

Appendix

Table 1. Summary of retrospective PCNSL studies

Study	Pts. [n]	Median Age [years]	ECOG score	Treatment	ORR [%]	Median OS [months]	Median PFS [months]
Madle, 2015	81	66	0-1 67%	cTx[1]+/-R +/- ASCT +/-	75%	49	50
Dalia, 2014	89	61	0-1: 61%	HD-MTX+/- +/-R+/-Rad+/- i.th.	n/a	35	9
Holdhoff, 2014	54	65	n/a	R-HD-MTX		16	5
	27	66		HD-MTX		n/r	27
Kellog[2], 2014	45	59[3]	n/a	HD-MTX; MPV+/-R [4]	n/a	9	n/a
Kim, 2014	40	55	0-1: 55%	MVP +/- ASCT +/- Rad	80	n/r (15)	n/a
Shibamoto, 2014			0-2:	HD-MTX containing			
1985-1994	466	60	52%	regimen	n/a	18	9
1995-2004	273	61	65%	(84%) +/-		26	20
2005-2009	315	63	73%	Rad (90%)		35	21
Lee, 2014	38	69	n/a	Modified EORTC[5]	74	43	18.1
Gregory, 2013	120	65	0-1: 33%	HD-MTX-R HD-MTX-Ara-C R-MPV +/- Rad	n/a	n/r (30)	n/a
Schorb, 2013	105	54	n/a	HD-MTX-Ara-C-Th (77%) + ASCT +/- Rad	95	47	85
Ghesquièrs, 2013	91	59	0-1: 58%	cTx +/- Rad[6]	68	33	n/a
Birnbaum, 2012	19	66	n/a	HD-MTX-I	90	n/r (30)	18
	17	66	n/a	R-HD-MTX-I	100	n/r (18 mo)	30
Taguchi, 2012	35	69	0-1: 26%	Rad	n/a	20	n/a
Welch, 2012	24	82	n/a	MPV Ara-C Rad.	63	8	7
Cobert, 2010	121	63	n/a	HD-MTX	85	84	38

Abbreviations: Pts: patients; ECOG score: Eastern Cooperative Oncology Group score; ORR: overall response rate; OS: overall survival; PFS: progression free survival; cTX: chemotherapy; R: rituximab; ASCT: autologous stem-cell transplantation; HD-MTX, high-dose methotrexate; Rad, radiation; i.th, intrathecal

therapy; n/a, not available; n/r, not reached; MPV: methotrexate, procarbazine, vincristine; Ara-C, cytarabine; Th, thiotepa; I: ifosfamide.

[1]9 diverse chemotherapy protocols (inclusive Bonner protocol, Freiburger protocol etc.);

[2]Including primary and secondary CNS lymphoma;

[3]Mean age;

[4]17% M; 29% MPV+/- R;

[5]EORTC protocol: MTX, ranimustine, procarbazine, methylprednisolone + i.th. cytarabine and methotrexate;

[6]C5R protocol 45%; HD-MTX + CHOP-like regimen 18%; HD-MTX +HD cytarabine+ CHOP-like regimen 10%; HD-MTX + alkylating agent 16%; CHOP-like regimen 4%; Alkylating agent 7%; CTx+Rad 73%.

Table 2. Summary of prospective PCNSL studies

Study	Pts. [n]	Median Age [years]	ECOG score	Treatment	ORR [%]	Median OS [months]	Median PFS [months]
Omuro, 2015	32	57	n/a	R-MPV +/- ASCT	97	n/r (45)	n/r (45)
Pulczynski, 2015	66	64	0-1: 55%	HD-MTX based regimen[1]	91	n/r (22)	n/a
Wang, 2014	21	52	67	HD-MTX+ Ara-C	68	n/r (27.5)	n/r (27.5)
Wang, 2014	20	53	55	HD-MTX+Te	74	n/r (27.5)	n/r (27.5)
Wu, 2014	8	42	n/a	FTD + i.th + Rad	87	n/r (30)	30
Morris, 2013	52	60		R-MPV + Rad + Ara-C	95	79	39
Rubenstein, 2013	44	61	0-1: 82%	HD-MTX TeR + EAra-C	77	n/r (59)	29
Kasenda, 2012	43	54	n/a	cTx+ ASCT +/- Rad		104	104*
Ferreri, 2011	20	57	n/a	HD-MTX +Ara-C+Th +Rad	30	26	n/a
Fritsch, 2011	28	75	n/a	R-MPL	72	17	16
Chamberlain, 2010	40	61.5	n/a	R-HD-MTX	70	29	21
Thiel, 2010	318	63	n/a	HD-MTX +/- I -/+ Rad	54	21	n/a

Abbreviations: Pts: patients; ECOG score: Eastern Cooperative Oncology Group score; ORR: overall response rate; OS: overall survival; PFS: progression free survival; n/r: not reached; R: rituximab; MPV: methotrexate, procarbazine, vincristine; ASCT: autologous stem-cell transplantation; HD-MTX: high-dose methotrexate; Ara-C: cytarabine; Te: temzolomide; F: fotemustine; T: teniposide; D: dexamethasone; i.th, intrathecal therapy; Rad, radiation; E: etoposide; cTx: chemotherapy; Th, thiotepa; R-MPL: rituximab, methotrexate, procarbazine, lomustine; I: ifosfamide.

[1]Combination chemotherapy consisted of: rituximab, methotrexate, ifosfamide, dexamethasone, vincristine, cyclophosphamide, vindesine, cytarabine +/- temozolomide and intrathecale cytarabine;

*PFS for per-protocol-group.

References

1. Birnbaum T, Stadler EA, von Baumgarten L, Straube A: Rituximab significantly improves complete response rate in patients with primary CNS lymphoma. J Neurooncol. 109. 285-291 (2012)

2. Chamberlain MC, Johnston SK: High-dose methotrexate and rituximab with deferred radiotherapy for newly diagnosed primary B-cell CNS lymphoma. Neuro Oncol. 12. 736-744 (2010)

3. Cobert J, Hochberg E, Woldenberg N, Hochberg F: Monotherapy with methotrexate for primary central nervous lymphoma has single agent activity in the absence of radiotherapy: a single institution cohort. J Neurooncol. 98. 385-393 (2010)

4. Dalia S, Forsyth P, Chavez J, Price S, Shah B, Bello C, Sokol L, Pan E, Sotomayor E, Lee JH, Fisher K, Jaglal M: Primary B-cell CNS lymphoma clinicopathologic and treatment outcomes in 89 patients from a single tertiary care center. Int J Hematol. 99. 450-456 (2014)

5. Ferreri AJ, Licata G, oppoli M, Corazzelli G, Zucca E, Stelitano C, Zaja F, Fava S, Paolini R, Franzin A, Politi LS, Ponzoni M, Reni M: Clinical relevance of the dose of cytarabine in the upfront treatment of primary CNS lymphomas with methotrexate-cytarabine combination. Oncologist. 16. 336-341 (2011)

6. Fritsch K, Kasenda B, Hader C, Nikkhah G, Prinz M, Haug V, Haug S, Ihorst G, Finke J, Illerhaus G: Immunochemotherapy with rituximab, methotrexate, procarbazine, and lomustine for primary CNS lymphoma (PCNSL) in the elderly. Ann Oncol. 22. 2080-2085 (2011)

7. Gregory G, Arumugaswamy A, Leung T, Chan KL, Abikhair M, Tam C, Bajel A, Cher L, Grigg A, Ritchie D, Opat S: Rituximab is associated with improved survival for aggressive B cell CNS lymphoma. Neuro Oncol. 15. 1068-1073 (2013)

8. Ghesquières H, Drouet Y, Sunyach MP, Sebban C, Chassagne-Clement C, Jouanneau E, Honnorat J, Biron P, Blay JY: Evidence of time-dependent prognostic factors predicting early death but not long-term outcome in primary CNS lymphoma: a study of 91 patients. Hematol Oncol. 31. 57-64 (2013)

9. Holdhoff M, Ambady P, Abdelaziz A, Sarai G, Bonekamp D, Blakeley J, Grossman SA, Ye X: High-dose methotrexate with or without rituximab in newly diagnosed primary CNS lymphoma. Neurology. 83. 235-239 (2014)

10. Kasenda B, Schorb E, Fritsch K, Finke J, Illerhaus G: Prognosis after high-dose chemotherapy followed by autologous stem-cell transplantation as first-line treatment in primary CNS lymphoma - a long-term follow-up study. Ann Oncol. 23. 2670-2675 (2012)

11. Kellogg RG, Straus DC, Karmali R, Munoz LF, Byrne RW: Impact of therapeutic regimen and clinical presentation on overall survival in CNS lymphoma. Acta Neurochir (Wien). 156. 355-365 (2014)

12. Kim YR, Kim SH, Chang JH, Suh CO, Kim SJ, Kim Y, Hwang DY, Jang JE, Hyun SY, Cheong JW, Min YH, Kim JS: Early response to high-dose methotrexate, vincristine, and procarbazine chemotherapy-adapted strategy for primary CNS lymphoma: no consolidation therapy for patients achieving early complete response. Ann Hematol. 93. 211-209 (2014)

13. Lee SY, Okoshi Y, Kurita N, Seki M, Yokoyama Y, Maie K, Hasegawa Y, Chiba S: Prognosis factors in Japanese elderly patients with primary central nervous system lymphoma treated with a nonradiation, intermediate-dose methotrexate-containing regimen. Oncol Res Treat. 37. 378-383 (2014)

14. Madle M, Krämer I, Lehners N, Schwarzbich M, Wuchter P, Herfarth K, Egerer G, Ho AD, Witzens-Harig M: The influence of rituximab, high-dose therapy followed by autologous stem cell transplantation, and age in patients with primary CNS lymphoma. Ann Hematol. 94. 1853-1857 (2015)

15. Morris PG, Correa DD, Yahalom J, Raizer JJ, Schiff D, Grant B, Grimm S, Lai RK, Reiner AS, Panageas K, Karimi S, Curry R, Shah G, Abrey LE, DeAngelis LM, Omuro A: Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. J Clin Oncol. 31. 3971-3979 (2013)

16. Omuro A, Correa DD, DeAngelis LM, Moskowitz CH, Matasar MJ, Kaley TJ, Gavrilovic IT, Nolan C, Pentsova E, Grommes CC, Panageas KS, Baser RE, Faivre G, Abrey LE, Sauter CS: R-MPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma. Blood. 125. 1403-1410 (2015)

17. Pulczynski EJ, Kuittinen O, Erlanson M, Hagberg H, Fosså A, Eriksson M, Nordstrøm M, Østenstad B, Fluge Ø, Leppä S, Fiirgaard B, Bersvendsen H, Fagerli UM: Successful change of treatment strategy in elderly patients with primary central nervous system lymphoma by de-escalating induction and introducing temozolomide maintenance: results from a phase II study by the Nordic Lymphoma Group. Haematologica. 100. 534-540 (2015)

18. Rubenstein JL, Hsi ED, Johnson JL, Jung SH, Nakashima MO, Grant B, Cheson BD, Kaplan LD: Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). J Clin Oncol. 31. 3061-3068 (2013)

19. Schorb E, Kasenda B, Atta J, Kaun S, Morgner A, Hess G, Elter T, von Bubnoff N, Dreyling M, Ringhoffer M, Krause SW, Derigs G, Klimm B, Niemann D, Fritsch K, Finke J, Illerhaus G: Prognosis of patients with primary central nervous system lymphoma after high-dose chemotherapy followed by autologous stem cell transplantation. Haematologica. 98. 765-770 (2013)

20. Shibamoto Y, Sumi M, Onodera S, Matsushita H, Sugie C, Tamaki Y, Onishi H, Abe E, Koizumi M, Miyawaki D, Kubota S, Ogo E, Nomiya T, Takemoto M, Harada H, Takahashi I, Ohmori Y, Ishibashi N, Tokumaru S, Suzuki K: Primary CNS lymphoma treated with radiotherapy in Japan: a survey of patients treated in 2005-2009 and a comparison with those treated in 1985-2004. Int J Clin Oncol. 19. 963-971 (2014)

21. Taguchi S, Hamamoto Y, Fujii T, Ochi T, Harada H, Ohnishi T, Mochizuki T: Prognosis of primary central nervous system lymphoma treated with radiotherapy alone. Jpn J Radiol. 30. 806-810 (2012)

22. Thiel E, Korfel A, Martus P, Kanz L, Griesinger F, Rauch M, Röth A, Hertenstein B, von Toll T, Hundsberger T, Mergenthaler HG, Leithäuser M, Birnbaum T, Fischer L, Jahnke K, Herrlinger U, Plasswilm L, Nägele T, Pietsch T, Bamberg M, Weller M: High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. Lancet Oncol. 11. 1036-1047 (2010)

23. Wang XX, Huang HQ, Bai B, Cai QQ, Cai QC, Gao Y, Xia YF, Xia ZJ, Jiang WQ: Clinical outcomes of patients with newly diagnosed primary central nervous system lymphoma are comparable on treatment with high-dose methotrexate plus temozolomide and with high-dose methotrexate plus cytarabine: a single-institution experience. Leuk Lymphoma. 55. 2497-2501 (2014)

24. Welch MR, Omuro A, Deangelis LM: Outcomes of the oldest patients with primary CNS lymphoma treated at Memorial Sloan-Kettering Cancer Center. Neuro Oncol. 14. 1304-1311 (2012)

25. Wu JJ, Wang XH, Li L, Li X, Zhang L, Sun ZC, Fu XR, Ma W, Chang Y, Zhang XD, Han LJ, Zhang MZ: Fotemustine, teniposide and dexamethasone in treating patients with CNS lymphoma. Asian Pac J Cancer Prev. 15. 4733-4738 (2014)