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Case Report

A Retrospective Study of Treatment Results of Blood-Brain Barrier Disruption (BBBD) Based Immunochemotherapy Combined with Autologous Stem Cell Transplantation (ASCT) in Patients with Primary Central Nervous System Lymphoma (PCNSL)

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Abstract

Primary central nervous system lymphoma PCNSL is an aggressive disease with increasing incidence. For unknown reason its incidence rates have been steadily increasing in Western societies for several decades especially among elderly population. PCNSL is a chemo sensitive disease with a challenging location behind blood-brain barrier. One treatment option is the blood-brain barrier opening with intra-arterial hypertonic mannitol before chemotherapy infusion to achieve efficient chemotherapy concentrations to eradicade tumor. In this study was analysed the outcome of 53 PCNS patients treated with five-drug regimen in conjunction with blood-brain barrier disruption (BBBD) followed by autologous stem cell transplantation outside our prospective phase II study in Oulu University Hospital between 1/2011 - 12/2021. Here we report the outcome of 53 patients treated outside the study protocol. Staging methods and follow-up procedures were in principal performed according to standard PCNSL guidelines. In the first-line treatment, 2- and 5-years progression free survival was 61.1% in the intention-to-treat population. In the relapse population 2-year and 5-year, PFS were correspondingly 56% and 42%. 2-and 5 years disease specific survival rates were 86.3% and 81% in the first-line population and 62.4 % and 52% in the relapsed setting, respectively. Based on analysed retrospective data blood-brain barrier disruptive treatment is a promising treatment method in this rare and aggressive disease.

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare and aggressive extra-nodal non-Hodgkin lymphoma affecting the brain, spinal cord, cerebrospinal fluid (CSF), cranial and spinal nerves, and vitreoretinal compartment [1,2]. Initiation of treatment is time sensitive for optimal neurologic recovery and disease control in primary central nervous system lymphoma (PCNSL) [3]. The WHO classification of lymphoid neoplasm recognizes this distinct entity as primary diffuse large B-cell lymphoma of the central nervous system (CNS), representing the overwhelming majority of PCNSL [4]. PCNSL accounts for up to 1% of all NHL cases and approximately 2% of all primary CNS tumors, but the incidence rates of PCNS are increasing [5]. The prognosis of PCNSL has been dismal but in recent years there has been considerable progress in treatment results. Current standard of therapy is intravenous high-dose methotrexate based multi agent chemotherapy combined with consolidative high dose chemotherapy followed by autologous hematopoietic stem cell transplantation (ASCT) [6-12]. The role of consolidative radiotherapy is contraversal. Ferreri et al has demonstrated that the relative efficacy of WBRT (whole brain radiotherapy) and ASCT did not alter over time, showing a 7-year overall survival close to 60% for both consolidation arms. The negative effect of WBRT on some cognitive functions and the positive effect of ASCT on both cognitive functions and quality of life (QoL) were confirmed with longer follow-up [13]. The challenge in PCNSL is its location behind the blood-brain barrier that prevents penetration of the most effective lymphoma chemotherapeutics into the central nervous system [14]. For this reason one treatment option is to open the blood-brain barrier with intra-arterial hypertonic mannitol infusion (BBBD therapy) before chemotherapy infusion to achieve efficient drug concentrations to eradicade tumour cells [6, 15, 16, 17, 18]. BBBD therapy has been established in Oregon Health and Science University by Professor Edward Neuwelt [16]. The therapy modality was established in Oulu University Hospital in January 2007 and between 2007-2011 the original treatment regimens developed by professor Neuwelt were used. Since 2012 we have used intensified treatment regimens including 5-drug treatment regimen given with three to four week intervals. A retrospective analyse of our treatment results was published in Journal of Neuro-oncology in 2017 [17]. This publication included only a few patients treated with five-drug regimen. The results were promising though the small number of patients and a short follow-up time prevented making firm conclusions. Since this report, we have treated 78 patients with this five-drug regimen. From these 25 patients were treated in our prospective phase II study, the first results of which have been just published [18]. Here we report a retrospective analyse of 53 patients treated outside the study protocol. Main reasons to treat outside the protocol were age, co-morbidities or impaired performance status.

Materials and Methods

Patient, staging and treatment

This is a retrospective study analysing treatment outcomes of PCNSL patients Here we report the results of treatment results of our PCNSL patients treated outside clinical study protocol with a five-drug regimen. We find the results still very promising and worth of further evaluation. At the moment we have published our phase II study for the first line patients and decided to expand the first-line treatment population and aim to assess a third study group for elderly patient with a modified induction treatment. Based on analysed retrospective data blood-brain barrier disruptive treatment is a promising treatment method in this rare and aggressive disease. Patient demographics are given in Table 1. There were 43 patients with first-line treatment and 10 patients with relapse setting. Altogether 12/43 of first-line patients

had refractory disease. Disease progression during treatment was observed in 6 patients. Three of them received Bonn treatment [19], one patient was treated based on Nordic elderly protocol [20] and two patients received MATRix-treatment before proceeding to the bbbd treatment [12]. Biopsy-proven histological diagnosis or cerebrospinal fluid (CSF) cytological diagnosis of DLBCL were required. Feasibility to treatment was evaluated by physical examination and efficient liver, renal and cardiac function. HIV, HBV and HCV serology were tested. Contrast-enhanced whole-brain magnetic resonance imaging (MRI), whole-body computed tomography scanning (CT), testicular ultrasound for male patients, ophthalmological assessment (including slit-lamp examination) and audiogram were performed to all patients. The medical history of the participants was reviewed by an anaesthesiology specialist to evaluate their suitability for the BBBD treatment. Cardiac ultrasound was performed if necessary. Risk groups were defined according to the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic scoring system [21]. At the time of the diagnosis a lumbar puncture was considered too risky for 19 (35.8%) patients and therefore the data about spinal fluid involvement is lacking from these patients. Almost all patients received cytoreductive chemotherapy before proceeding to BBBD treatment with one cycle Bonn A (n=18), MATRix (n=25), R-CHOP-Mtx (n=1) or Mtx-Temozolomide (n=2) [19, 22]. After publishing the results of IELSG-32 study, MATRix regimen was adopted to induction scheme [22]. Seven patient with relapsed disease did not receive cytoreductive treatment before proceeding to BBBD treatment. After confirmed radiological response to cytoreductive chemotherapy patients proceeded to BBBD treatment. Patient's received four to six BBBD therapy cycles with five-drug regimen including rituximab, methotrexate, carboplatin, etoposide and cyclophosphamide according to treatment response. The details of doses and blood-brain barrier disruption procedure have been described in our previous publication [18]. After induction therapy transplant-eligible patients were consolidated with BCNU-thiotepa high- dose chemotherapy regimen followed ASCT. Patients with progressive disease proceeded to WBRTor palliative treatment. Patients with intraocular lymphoma were treated with intravitreal methotrexate and rituximab injections as described by Yeh and Wilson [23].

Sex	N (%)
Male	33 (62.3)
Female	20 (37.7)
Age at the diagnosis	median (mean + SD)
Years	62.6 (31-77)
Performance status (ECOGa)	N (%)
0	6 (11.3)
1	14 (24.4)
2	17 (32.1)
3	11 (20.8)
4	5 (9.4)
MSKCCb risk group	N (%)
0 (age <50 years)	10 (18.9)
1 (age ≥50 years and KPSc ≥70%)	13 (24.5)
2 (age ≥50 years and KPSc <70%)	30 (56.6)
Eye involvement	N (%)
Yes	18 (34)
No	24 (45.3)
Missing data	11 (20.8)
Neutropenic sepsis	N (%)
Yes	27 (50.9)

No	26 (49.1)
Spinal Involvement	N (%)
Yes	10 (18.9)
No	24 (45.3)
Missing data	19 (35.8)
Treatment phase	N (%)
Primary	31(58.5)
Relapsed	10 (30.2)
Primary refractory	12(11.3)
Cytoreductive induction treatment	N (%)
MATRix	25 (47.2)
Bonn treatment	18 (40%)
No induction treatment	7 (13.2)
R-CHOPc-HDMtxd	1 (1.9)
Mtx-temozolomide	2 (3.8)
ASCTe	N (%)
Yes	33 (62.3)
No	20 (37.7)
Reasons for discontinuation of the treatment	N (%)
No discontinuation	36 (67.9)
Diasease progression	8 (15.1)
Impaired EGOC status	6 (11.3)
Adverse event	2 (3.9)
Patient preference	1 (1.9)
ECOGa, Eastern Cooperative Oncology Group, MSKCCb, Memorial Sloan Kettering Cancer Center, ASCTe, Autologous Stem cell Transplantation, CHOPc, Cyclophosphamide, doxorubicin, vincristine and prednisone, HDd, High-dose	

Table 1: Patient demographics.

Response evaluation and follow-up

Tumor response for treatment was evaluated with magnetic resonance imaging (MRI) before each course of BBBD treatment and one month after ASCT [24]. In the case of residual enhancing MRI positive lesions the significance of findings was evaluated with brain positron emission tomography computed tomography (PET-CT) scanning since 2018. There were nine such patients [25]. Overall survival (OS) was calculated from the date of the BBBD treatment initiation to the date of death from any cause. Disease specific survival (DSS) was calculated from the date of the treatment initiation to the date of death from lymphoma. Progression-free survival (PFS) was calculated from the date of BBBD treatment initiation to the date of last follow-up, lymphoma progression, or death, whichever occurred first. Time to progression (TTP) was calculated from the date of treatment initiation to the date of lymphoma progression. Intention to treat population (ITT) was defined to a population for analysing results where all participants were included in the statistical analysis and analysed according to the group they were originally assigned, regardless of what treatment they received. In the analysis of per-protocol treated patients (PPT), participants were only included if they received induction therapy proceeding to high-dose treatment followed by autologous stem cell transplantation. Refractory disease was defined as disease progression during to first-line treatment and within six months of the end of the treatment. Relapsed disease was defined with recurrence over six months after completed treatment. Disease recurrence more than six months after the completed treatment was defined as a relapsed disease. In final analyses, refractory and relapsed patients were combined. Follow-up visits were planned for every three months up to two years and then every six months until five years from the initiation of the treatment.

Statistics

Basic demographics were expressed as means and standard deviations or frequencies and percentages. The Kaplan–Meier method was used to estimate survival rates with 95% confidence intervals (CIs) for outcome variables. All statistics were performed using IBM SPSS software (IBM SPSS Statistics for Windows, Version 26.0., IBM Corporation, Armonk, NY).

Results

Patient population

A total of 53 patients outside the prospective study protocol were collected in patient registry data between 1/2012-12/2021. Patient demographics and MSCKK risk groups are presented in Table 1. Altogether 43 patients were treated in first-line and 10 16 patients in relapsed setting. 12/43 of first line patients were determined to have been refractory to previous intravenous therapy. The Mean age was 64.3 years for first-line patients and 60.2 years for relapsed patients. During the first line treatment 6/53 patients and 3/53 relapsed patients were at age of 70 or older. 33/53 patients received ACST and 20 patients did not. One patient declined treatment due to religious reasons before consolidative ASCT. With one patient there were difficulties in collecting stem cells. Eight patients due to disease progression and six patients due to impaired l performance status could not proceed to ASCT.

Toxicity

BBBD treatment is chemo intensive treatment and haematological toxicity was common and in line with our previous reports [18]. Despite of the frailer patient population compared to BBBD study population, treatment-related mortality rate did not differ. One patient died due to neutropenic sepsis in complete remission after fourth BBBD treatment and one after first BBBD treatment. Twenty-seven patients (50.9%) had s febrile neutropenia during the treatment course. One patient discontinued treatment due to infection adverse event and impaired physical status and three patients because of inadequate neurocognitive recovery, respectively.

Efficacy ITT, PPT

In the first line treatment 2-and 5 year OS were 83.5% and 78.3%, respectively. In the relapsed setting, the values were correspondingly 59.4% and 42.5% [Figure 1A]. Disease specific survival was 86.3% and 78.3% in first-line compared to 62.4% and 52% in relapse setting [Figure 1B]. 2-and 5 year PFS were 61.1% and 61.1% in first-line and correspondingly 56% and 42% in relapsed setting [Figure 1C]. TTP in first-line were 63.6% at 2- and 5 years, 56%, and 42% in relapsed setting [Figure 1 D]. Per protocol treated patients in the first-line treatment 2-and 5 year OS were 94.1% and 87.8% and respectively 57.6% in relapse setting 57.6% [Figure 2A]. Disease- specific survival rates at 2 and 5 years were 94.1% and 84.8% in first-line treatment arm and 57.6% and 57.6% in the relapsed setting [Figure 2B]. 2 and 5 year PFS per protocol treated was 71.4 in first-line and correspondingly in relapsed setting 50.2% [Figure 2C]. In the line per protocol treated TTP was 63.6% in first-line at the 2-and 5 five years and 56% and 42% in relapsed setting [Figure 2D].

Discussion

In this retrospective real-world study we have reported an expanded cohort of 53 PCNSL patients treated in first-line (n=43) or relapsed setting (n=10) with five-drug regimen in conjunction with BBBD followed by high- dose treatment and ASCT in Oulu University Hospital. In this expanded cohort with longer follow-up period, the results still seem to be very promising. In the first-

line treatment, 2- and 5-years progression free survival was 61.1% in the intention-to-treat population. In the relapse population 2-year and 5-year, PFS were correspondingly 56% and 42%. 2-and 5 years disease specific survival rates were 86.3% and 81% in the first-line population and 62.4 % and 52% in the relapsed setting, respectively. PCNSL still represents a challenge in therapeutic point of views due to blood brain barrier (BBB) that prevents to achieve therapeutic concentrations of most common lymphoma chemotherapeutics [14,17]. A major advantage of the BBBD technique in comparison to conventional intravenous dosing of chemotherapeutic agents is the increased drug delivery to CNS [6].

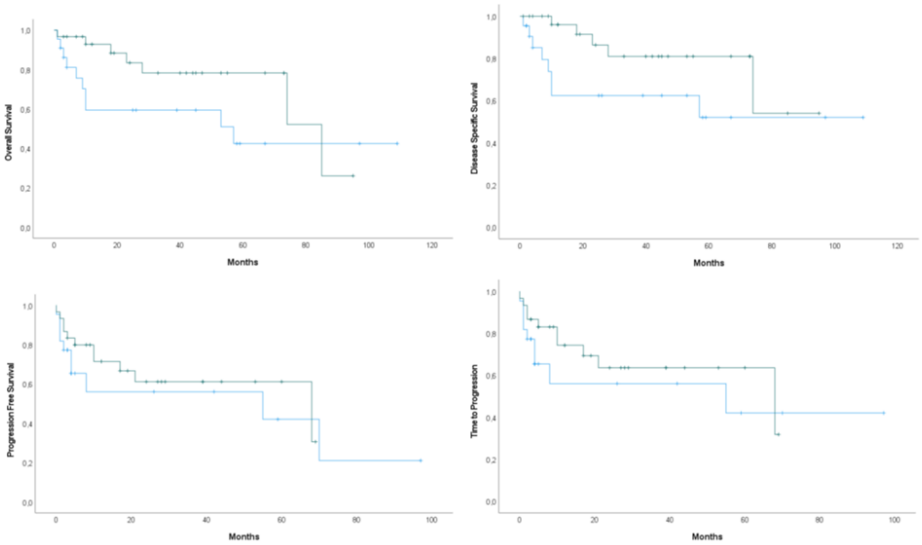

Figure 1: Intention to treat population. 1A. 2-and 5 year overall survival 83.5% and 78.3% in first-line and 59.4% and 42.5% in relapsed and refractory patient setting. 1B. 2-and 5 year disease-spesific survival 86.3% and 81% in first-line and 62.4% and 52% in relapsed and refractory patient setting. 1C. 2-and 5 year progression-free survival 61.1% in first line and 56% and 42% in relapsed and refractory setting. 1D. 2-and 5 year time to progression 63.6% in first- line and 56% and 42% in relapsed and refractory setting.

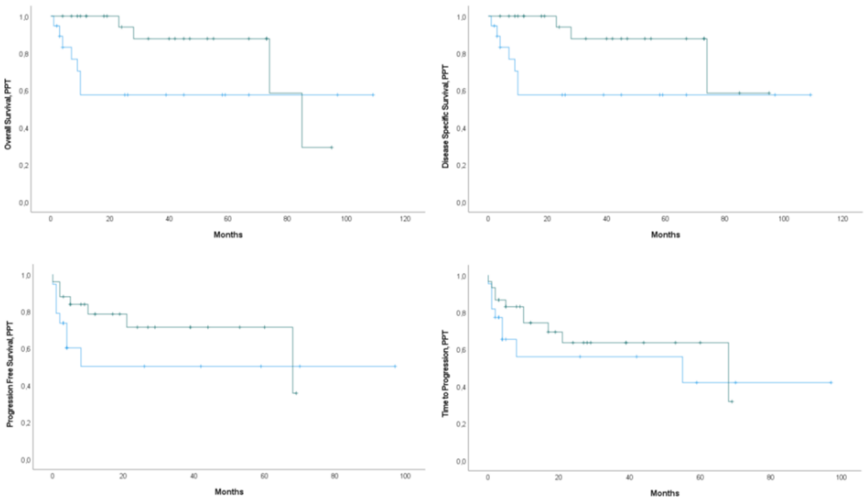

Figure 2: Per protocol treated population. 2A. 2-and 5 year overall survival 94.1% and 87.8% in first-line and 57.6% in relapsed and refractory patient setting. 2B. 2-and 5 year disease-spesific survival 94.1% and 84.8% in first-line and 57.6% in relapsed and refractory patient setting. 2C. 2-and 5 year progression-free survival 71.4% in first line and 50.2% in relapsed and refractory setting. 2D. 2-and 5 year time to progression 63.6% in first line and 56% and 42% in relapsed and refractory setting.

We have intensified the original BBBD protocol developed by Angelov et al. by including an induction with one cycle of cytoreductive intravenous Bonn-or Bonn-like regimen and since 2018 promising MATRix treatment before proceeding to BBBD treatment and and HD + ASCT consolidation in the protocol [6,17,18,19,22]. Patients with high tumor volume tend to recover slowly from their first BBBD cycle without preceding intravenous cytoreduction and by using one cycle of multiagentchemotherapy we could avoid the prolonged recovery period. The another reason for this decisions was logistic, because taking into account the multidisciplinary team of BBBD treatment, arranging the treatment takes some time and we wanted to avoid treatment delays. These results are consistent with our previously published analyses with prospective and retrospective studies, where the intensified regimen seemed to improve treatment efficacy [17,18]. In our prospective analysis, 2-year PFS rate of 70.3% in the ITT population parallels with the 2-year PFS rate of 61% in the IELSG-32 study MATRix arm [22]. In this retrospective analyses chemotherapy-related toxicity and malignant condition-related complications were comparable to our previous retrospective study report and our prospective study data [17,18]. Two patients died due to neutropenic sepsis. High treatment-related toxicity and mortality are also common to most other first-line PCNSL chemotherapy regimens and our results are consistent with them [12,22,26,27]. Our population also represents a challenging one, with several patients with the age above 70 and poor performance status. Whether smaller drug doses would suffice for a comparable efficacy, requires further studies. As PCNSL is a highly proliferating malignancy causing rapidly developing and potentially permanent neurological defects, urgent therapy initiation is needed to optimize neurological recovery [1,28-30]. This is challenging considering the logistical aspects of gathering the multidisciplinary team for the BBBD treatment. PCNSL is a rare disease. For unknown reason the incidence has been steadily increasing in the Western societies for several decades [5-11]. PCNSL is a chemo sensitive disease with a challenging location behind blood-brain barrier which blocks the penetration of most effective lymphoma chemotherapeutics to the tumor. High-dose metothrexate combined with other (immuno) chemotherapeutics is currently considered as standard therapy.

In a randomised IELSG-32 study MATRix regimen (rituximab, methotrexate, cytarabine and thiotepa) was superior compared to methotrexate, cytarabine or methotrexate, cytarabine thiotepa combination in terms of both response rate, progression free survival and overall survival [12]. After induction treatment, therapy is usually consolidated with either WBRT or ASCT. According to second randomisation in IELSG-32 studies, these options seem to have comparative efficacy. Long-term side effects of the whole brain irradiation consists of cognitive decline and progressive dementia [22]. Updated 7-years data confirmed these findings. Patients who received WBRT experienced impairment in attentiveness and executive functions, whereas patients undergoing ASCT experienced improvement in these functions as well as in memory and quality of life [13]. For these reasons ACST is the preferred consolidation method in transplant-eligible patients. First results of an international randomized phase III trial (MATRix/IELSG43) confirm the role of consolidative ASCT in PCNSL after induction treatment [31]. In aggressive systemic lymphomas, relapses occur usually during the first 24 months. Patients staying in remission for five years from the end of therapy are regarded to be cured. However, despite its aggressive behaviour of PCNSL seems to have also a continuous relapsing pattern [15] like in low-grade lymphomas. Relapses are detected even 10 years after successful treatment [32, 33]. For this reason, many studies reporting the results after short follow-up time overestimate the number of patients actually cured from PCNSL. In Oulu University Hospital, we have an ongoing prospective study for first-line PCNSL patients under the age of 70 years. Here we report patients treated outside that study. They were not recruited to the study because of age over 70 years, comorbidities, impaired ECOG performance status or declined cognitive performance status preculed their ability to give an informed consent. Altogether 24/53 patients were treated in experimental setting before the trial started. Afterwards we analysed all those patients and 10/24 of those patients did not meet the inclusion criteria. For the aforesaid reasons analyses describe treatment result of BBBD therapy in a very dismal patient population. Despite these adverse prognostic features, we found that we have achieved satisfactory outcome in terms of overall,-disease free, progression free survival and time to progression. Notable with in line with our previous two studies, late relapses are extremely rare, In this study one patient had a relapse at 68 months treated in first-line and another at 55 months treated after a relapse.. This protocol is associated with remarkable number of cytopenias and infectious complications and two patient died in treatment-related complication, which is in line with toxicities with other regimens in this fragile patient population. Many patients with PCNSL with poor performance status during diagnosis still have a remarkable recovery potential [28,34-35]. For this reason, we have wanted to give our patients chance for curative therapy even if over half of our patients had a WHO performance score two or more at the time of diagnosis. When treating such a fragile and poor performance status patient population, it is natural that not all patient tolerate the therapy. Also, despite excellent tumor response, four patients discontinued the therapy because no neurocognitive recovery has happened. Some interruptions have been caused by cardiac problems usually arising during anaesthesia. For this reason, currently we use more strict inclusion criteria's for patients with a pre-existing cardiovascular disease, which should be stable before starting BBBD-therapy. A major drawback of this analysis includes its retrospective nature. In daily clinical practice, we have not performed neurocognitive surveillance. However, from

previous reports by Neuwelt and Doolittle et al. we can assume that this treatment regimen do not cause neurocognitive impairment [16,36]. Our ongoing phase II study will include more detailed, prospectively collected data of treatment-related adverse events, as well as neurocognitive surveillance. Despite these drawbacks, promising treatment outcomes reported here and should be verified in larger and prospective setting in the future.

Conclusions

Here we report the results of treatment results of our PCNSL patients treated outside clinical study protocol with a five-drug regimen. We find the results still very promising and worth of further evaluation. At the moment we have published our phase II study for the first line patients and desided to expand the first-line treatment population and aim to assess a third study group for elderly patient with a modifield induction treatment. Based on analyzed retrospective data blood-brain barrier distruptive treatment is a promising treatment method in this rare and aggressive diasease.

Conflict of interest and other ethics statements: The study was conducted according to the guidelines of the Declaration of Helsinki. The authors declare no conflict of interest.

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