

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: <http://www.tandfonline.com/loi/ilal20>


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To cite this article: Marcel Nijland, Anne Jansen, Jeanette K. Doorduijn, Roelien H. Enting, Jacoline E. C. Bromberg & Hanneke C. Kluin-Nelemans (2017): Treatment of initial parenchymal central nervous system involvement in systemic aggressive B-cell lymphoma, *Leukemia & Lymphoma*, DOI: [10.1080/10428194.2017.1285026](https://doi.org/10.1080/10428194.2017.1285026)

To link to this article: <http://dx.doi.org/10.1080/10428194.2017.1285026>

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ORIGINAL ARTICLE: CLINICAL

Treatment of initial parenchymal central nervous system involvement in systemic aggressive B-cell lymphoma

Marcel Nijland^a, Anne Jansen^b, Jeanette K. Doorduijn^c, Roelien H. Enting^d, Jacoline E. C. Bromberg^e and Hanneke C. Kluin-Nelemans^a

^aDepartment of Haematology, University Medical Centre Groningen, University of Groningen, Groningen, Netherlands; ^bDepartment of Neurology, Canisius-Wilhelmina Hospital, Nijmegen, Netherlands; ^cDepartment of Haematology, Erasmus MC Cancer Institute, Rotterdam, Netherlands; ^dDepartment of Neurology, University Medical Centre Groningen, University of Groningen, Groningen, Netherlands; ^eDepartment of Neurology, Erasmus MC, Rotterdam, Netherlands

ABSTRACT

Central nervous system (CNS) involvement in systemic B-cell non-Hodgkin lymphoma (B-NHL) at diagnosis (sysCNS) is rare. We investigated the outcome of 21 patients with sysCNS, most commonly diffuse large B-cell lymphoma, treated with high dose methotrexate (HD-MTX) and R-CHOP. The median number of cycles of HD-MTX and R-CHOP was 4 (range 1–8) and 6 (range 0–8), respectively. Consolidative whole brain radiotherapy (WBRT) was given to 33% (7/21) patients. With a median follow-up of 44 months the 3-year progression free survival (PFS) and overall survival (OS) were 45% (95%CI 34–56%) and 49% (95%CI 38–60%), respectively. Over 90% of patients had an unfavorable international prognostic index score, reflected by treatment-related mortality of 19% (4/21) and relapse-related mortality of 28% (6/21). The outcome of these patients was, however, unexpectedly good when compared to secondary CNS relapses. Prospective studies are needed to define the optimal treatment for patients with sysCNS, but its rarity might be challenging.

ARTICLE HISTORY

Received 24 October 2016
Revised 10 January 2017
Accepted 15 January 2017

KEYWORDS



Aggressive B-cell lymphoma; systemic; central nervous system; methotrexate; R-CHOP


Introduction

The risk of central nervous system (CNS) dissemination of aggressive B-cell lymphoma (B-NHL) is 5% [1]. High international prognostic index (IPI) score, kidney or adrenal gland involvement and diffuse large B-cell lymphoma (DLBCL) with dual expression of MYC and BCL2 by immunohistochemistry convey a high risk of CNS relapse [2,3]. In the majority, CNS involvement occurs during progression of the disease. Rarely, CNS dissemination is already present at initial diagnosis. Unlike the general favorable outcome of patients with primary CNS lymphoma (PCNSL) when treated with high dose methotrexate (HD-MTX), cytarabine and thiothepa [4–7], CNS relapse of aggressive B-NHL conveys a dismal prognosis [8,9]. Salvage regimens with relapsed PCNSL incorporating thiothepa and high dose chemotherapy followed by autologous stem cell transplantation (ASCT) showed an improved overall survival (OS) for these patients if initially responsive and subsequently eligible for intensive treatment [10,11].

It is unknown if the prognosis of concomitant systemic and parenchymal CNS B-NHL at diagnosis (sysCNS B-NHL) is different from secondary CNS lymphoma in the relapse setting. Given its rarity, data on treatment for sysCNS B-NHL are sparse and there is no established standard of care. Recent data from two studies suggest a beneficial effect of intensive chemotherapy followed by ASCT [12,13]. In both studies, ASCT was only offered to patients in complete remission (CR) (31%–50%). Furthermore, in one of the studies, anthracyclines – highly effective in systemic B-NHL – were only a minor part of the induction regimen [13]. Outcome of non-transplant strategies in sysCNS B-NHL was only explored in small series [14,15].

We observed an excellent response in a patient with sysCNS initially treated as if primary CNS with the European Organisation for Research and Treatment of Cancer (EORTC) regimen MBVP (methotrexate, etoposide, carmustine and prednisolone) [5]. In this patient, not only the CNS component responded well, but also

CONTACT Marcel Nijland  m.nijland@umcg.nl  Internist-Haematologist, Department of Haematology, University Medical Centre Groningen, Hanzeplein 1, 9713 GZ Groningen, Netherlands

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systemic involvement responded at the same time. Consequently, we continued after MBVP with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), and applied this regimen to the next series of patients. Simultaneously, another University Medical Center in the Netherlands combined R-CHOP alternating with HD-MTX, based upon the same observations.

Therefore, we retrospectively investigated the outcome of patients with sysCNS B-NHL treated in both centers with a combination of drugs effective for CNS and systemic involvement. None of these patients underwent ASCT.

Methods

Study design and patient identification

Clinical data on patients with sysCNS B-NHL were retrieved from the electronic databases of two referral medical centres in the Netherlands. All patients had newly diagnosed, histologically proven aggressive B-cell lymphoma. In case of transformed lymphoma, patients had not received prior therapy. CNS involvement was determined either by biopsy, magnetic resonance imaging (MRI) and/or CSF examination. Patients had been treated between 2000 and 2015. Patients should have received at least one cycle of HD-MTX. Both regimens start with a cycle of HD-MTX. The pathological assessment was performed by experienced hematopathologists. Since patients were treated according to best practice no medical ethical committee approval was required.

Treatment and follow-up

Initial assessment

Staging consisted of computed tomography scan of neck, chest, abdomen and pelvis, bone marrow biopsy, cerebrospinal fluid (CSF) examination with four-color flow cytometry (FCM), MRI brain, and further investigations if clinically indicated. A fluorodeoxyglucose (^{18}F -FDG) positron emission tomography scan was available for all patients treated at one of the medical centres. Systemic B-NHL was diagnosed by lymph node or tissue biopsies in all cases. CNS involvement was diagnosed either by brain biopsy or CSF flow cytometry in 58% (12/21) of patients. In 42% (9/21) neurological symptoms and parenchymal abnormalities on the MRI scan were considered sufficient for the diagnosis of CNS involvement. In 10% (2/21) CNS involvement presented as neurolymphomatosis. In all

patients the international prognostic index (IPI) was documented.

Treatment

Patients were treated according to one of two regimens. At the University Medical Centre Groningen a sequential regimen was adopted. Four cycles of MTX at a dose of 3 g/m^2 were given as part of the MBVP regimen, which also includes carmustine (100 mg/m^2 at day 4), teniposide (100 mg/m^2 at day 2 and 3) and prednisolone (60 mg/m^2 at day 1–5) [5]. Interim response evaluation was performed after completion of HD-MTX. Patients with a partial CNS remission received whole brain radiotherapy (WBRT) at this point. Patients subsequently continued for 6 cycles of R-CHOP after which end-of-treatment evaluation took place. R-CHOP was given as a combination of rituximab (375 mg/m^2 at day 1), cyclophosphamide (750 mg/m^2 at day 1), doxorubicin (50 mg/m^2 at day 1), vincristine (1.4 mg/m^2 at day 1 up to a maximal dose of 2 mg) and prednisolone (100 mg at day 1–5). At the Erasmus Medical Centre Rotterdam an alternating regimen was adopted, which consisted of 6 alternating cycles of HD-MTX at a dose of 3 g/m^2 and R-CHOP. Interim evaluation was performed after 3 cycles and end-of-treatment evaluation after completion of therapy. Patients with a partial remission (PR) of the CNS involvement received WBRT. In both regimens patients with leptomeningeal involvement received intrathecally methotrexate and/or cytarabine until complete clearance of the CSF as assessed by FCM. Furthermore, 4 patients in the alternating regimen received i.t. therapy without a positive CSF because of local practice.

Response assessment

Response was evaluated according to the 1999 consensus criteria for systemic NHL and the consensus criteria for PCNSL [16,17]. Tumor response was classified as CR, PR, stable disease (SD), or progressive disease (PD). Only patients in complete remission at CNS and systemic sites at the end of treatment were reported as a CR. Treatment related mortality (TRM) was defined as death during or ≤ 3 months after treatment.

Follow-up was completed until February 2016.

Statistical analysis

Duration of follow-up was calculated for all patients alive. The primary endpoints were OS and progression free survival (PFS). OS was defined as time from diagnosis until death (from any cause); PFS as the time

from diagnosis until relapse, progression or death (from any cause). Survival curves were estimated according to the Kaplan–Meier method. Between-group differences in OS and TTP were evaluated using the log-rank test. All categorical variables were expressed as counts and percentages. Where applicable, differences between groups were evaluated by chi-square for binary variables and independent T-tests for continuous variables. A two-tailed *p*-value of less than 0.05 indicated statistical significance. All analyses were performed using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY).

Results

Clinical characteristics

Between 2000 and 2015 21 sysCNS B-NHL patients were treated. Demographic data from the patients in the two treatment regimens are presented in Table 1. Diffuse large B-cell lymphoma composed the major histological B-NHL entity (66%). The median age was 54 years (range 19–71 years) with a slight female preponderance. Two-third of patients had a WHO performance score ≥ 2 and 91% of patients had an intermediate or high IPI-score. A large number of patients had lymphoma infiltration of organs known to convey a high risk of CNS relapse, like testicles (44% of patients at risk), bone (38%), kidney (19%) and breast (17% of patients

Table 1. Clinical characteristics at diagnosis of the 21 patients with concomitant systemic and parenchymal central nervous system B-cell non-Hodgkin.

Characteristics	Sequential MBVP/R-CHOP	Alternating MTX/R-CHOP
Patients (<i>n</i>)	10	11
Median age	54 (41–60)	59 (19–71)
Gender (M/F)	2/8	7/4
B-cell lymphoma		
Diffuse large B-cell lymphoma (%)	5 (50)	9 (82)
Iatrogenic immunodeficiency lymphoma (%)	2 (20)	1 (9)
Transformed marginal zone lymphoma (%)	2 (20)	0 (0)
Intravascular B-cell lymphoma (%)	1 (10)	1 (9)
Extra CNS involvement		
Testicular (%) ^a	0 (0)	4/7 (57)
Breast (%) ^a	2/8 (25)	0 (0)
Bone/bone marrow (%)	6 (60)	2 (18)
Kidney/lung (%)	4 (40)	0 (0)
Cerebrospinal fluid involvement (%)	4 (40)	4 (45)
Elevated LDH (%)	6 (60)	6 (54)
WHO performance		
1–2 (%)	2 (20)	5 (45)
3–4 (%)	8 (80)	6 (55)
IPI-score		
1 (%)	1 (10)	1 (9)
2–3 (%)	7 (70)	7 (64)
4–5 (%)	2 (20)	3 (27)

^aPercentage in patients at risk.

Testicular involvement can only be observed in male patients. Breast involvement can only be observed in female patients.

at risk). Besides parenchymal CNS, concomitant CSF involvement was present in 43% of patients.

Treatment

Thirteen patients (62%) completed therapy with only minor deviations. Two patients received less than 6 R-CHOP cycles. One patient had both a reduction in the number of MTX and R-CHOP cycles. Data on treatment intensity between the two treatment regimens are presented in Table 2. Detailed information on individual treatment and response assessment is shown in Supplementary Figure 1. The median number of HD-MTX cycles was 4 (range 1–8). Thirteen patients (62%) received concomitant intrathecal MTX. The median number of R-CHOP cycles was 6 (range 0–8). WBRT was given to 7 patients (33%), all because of persistent abnormalities on brain MRI. One patient received local radiotherapy on an extracranial site because of PR at the end of treatment. Besides the additional VP16 and BCNU in patients treated with MBVP, there was no significant difference between the two regimens.

Follow-up, response and survival

The median duration of follow-up of patients was 44 months (range 5–104). The overall response rate (ORR) at the end of treatment was 62%: CR 57% (*n* = 12) and PR 5% (*n* = 1). PD was noted in 19% (*n* = 4), whereas early TRM due to infectious complications was observed in 19% (*n* = 4). All infectious complications occurred during neutropenia. Two patients died as a consequence of an aspiration pneumonia due to neurogenic dysphagia. One patient developed a complicated clostridium difficile infection after prolonged treatment with ciprofloxacin. One patient died of a complicated meningitis (*Klebsiella pneumoniae*), which was not related to a previous lumbar puncture. One patient died 6 months after treatment as a result of cognitive deterioration.

Table 2. Treatment intensity in the 21 patients with concomitant systemic and CNS B-NHL at diagnosis.

Characteristics	Sequential MTX/R-CHOP	Alternating MTX/R-CHOP
Patients (<i>n</i>)	10	11
Median MTX cycles (<i>n</i>)	4 (2–6)	5 (1–8)
Median cumulative MTX dosing (gr)	12 (6–18)	15 (3–24)
Median i.t. MTX cycles (<i>n</i>) ^a	6 (4–10)	9 (4–13)
Median CHOP cycles (<i>n</i>)	6 (0–6)	6 (1–8)
Rituximab (%)	10 (100)	10 (90)
Additional chemotherapy	Teniposide Carmustine	n.a.
Radiotherapy in PR (%)	3 (30)	4 (36)

^aIn patients receiving i.t. therapy.

Number of i.t. cycles only described for patients receiving intrathecal therapy.

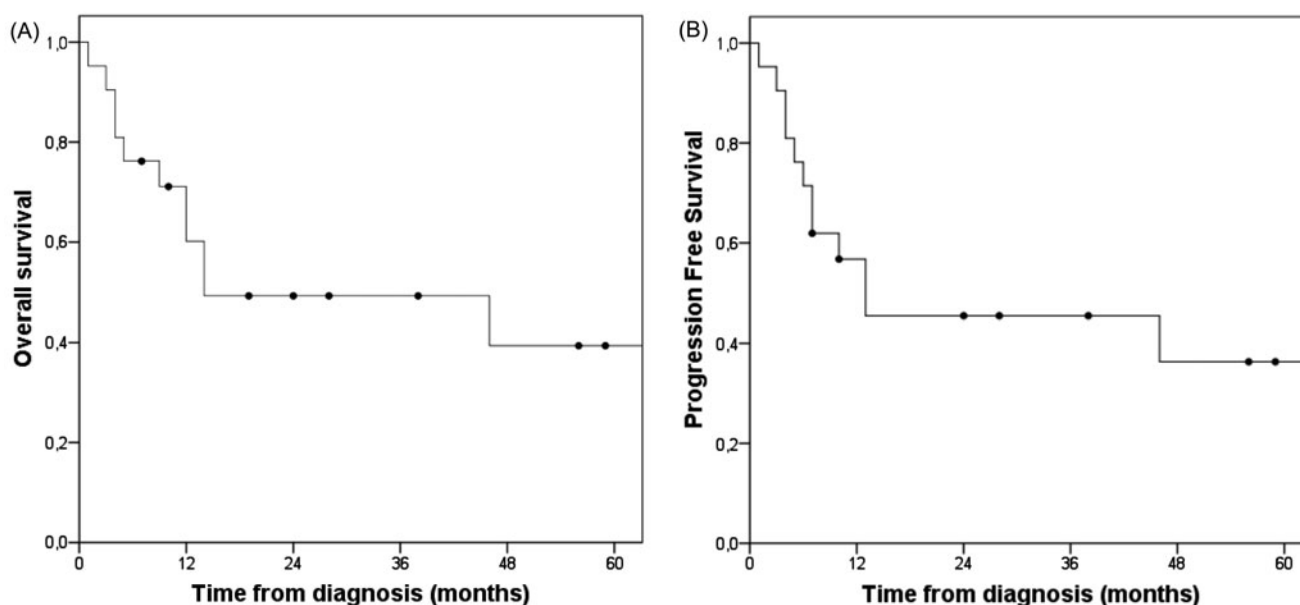


Figure 1. (A) OS and (B) PFS of 21 patients with concomitant systemic and parenchymal CNS B-NHL at diagnosis.

Three-year PFS and OS for the entire cohort were 45% (95%CI 34–56%) and 49% (95%CI 38–60%), respectively (Figure 1(A,B)). No significant differences in PFS and OS were found between both regimens (HR OS 1.25, 95%CI 0.38–4.2; p 0.72). Although statistical analysis showed no significant differences in outcome between the various variables due to the small number of patients, all patients ($n=3$) with IPI-score 0–1 were alive at follow-up, whereas all patients ($n=4$) with IPI-score 4–5 died within 2 years after diagnosis.

The combined incidence of refractory and relapsed sysCNS was 28% (6 of 21 patients). The relapse rate in patients achieving a CR was only 8% (1 of 12 patients), which is reflected by the plateau after 12 months in the PFS and OS curves (Figure 1(A,B)). Patients in CR/PR had a 3-year PFS and OS of 74% and 83%, respectively (Supplementary Figure 2(A,B)) The patient who relapsed did so within a year in the CNS. She subsequently received WBRT but died soon afterwards. The one patient in PR progressed after 8 months with both systemic and CNS involvement. He received no further therapy and died shortly thereafter. The four patients with PD all died within 6 months. The site of progression was systemic-only in two patients, CNS-only in one patient and concomitant systemic and CNS in one patient.

Discussion

By combining the results from two medical referral centres in the Netherlands, we performed the second largest retrospective study in patients with sysCNS

B-NHL. Findings from this study indicate that non-transplant regimens of HD-MTX and R-CHOP can be an effective treatment for sysCNS B-NHL. With a 3-year OS of 49% the outcome in our cohort is comparable to the more intensive regimen including ASCT, which is available to only a selected group of patients (5-year OS 41%) [13]. In one of the three studies with non-transplant regimens 4 out of 6 (67%) patients achieved a CR when treated with HD-MTX and R-CHOP. In a second study with HD-MTX, rituximab, cytarabine and idarubicin (R-IDARAM) 4 out of 10 (40%) patients achieved a CR. Median OS of both studies was 25.1 months and more than 30 months, respectively [14,18]. In a pilot study with dose-adjusted EPOCH (etoposide, cyclophosphamide, doxorubicin, vincristine, prednisone) plus rituximab 8 out of 8 patients achieved a CR [15]. Four patients underwent a consolidative autologous stem cell transplantation. With a median follow up of 11 months all patients were alive.

In most of our patients systemic involvement included one or more organs known to convey a high risk of CNS involvement in systemic B-NHL [1]. In particular 4 patients had renal involvement, which is the strongest risk factor for CNS relapse in DLBCL [3]. These findings suggest an early dissemination of a systemic B-NHL, rather than a systemic manifestation of a PCNSL. This might be important, since PCSNL has several pathological features that are only infrequently present in systemic DLBCL, such as a high incidence of mutations in *CD79B* and *MYD88*, loss of human leukocyte adhesion (HLA) molecules and frequent expression of the programmed death ligand 1 [19–21]. Despite its similarity with systemic B-NHL, the OS of sysCNS

B-NHL treated with HD-MTX and R-CHOP was better than expected and comparable to that of PCNSL and certainly not as bad as secondary relapsed CNS B-NHL treated with HD-MTX and cytarabine (Supplementary Table 1) [4–6,8].

The TRM in our cohort of 19% was high, and reflects the very unfavorable risk profile of our patients with 67% having a WHO performance of 3–4 and 14% being older than 65-years. Given the small numbers it cannot be answered whether the concomitant systemic involvement or additional R-CHOP played a role.

Despite the limited number of relapses, two observations were interesting: firstly, all but one patient who relapsed did so less than 6 months after the end of treatment. All other patients who failed did so during the early phase of treatment; secondly, in refractory and relapsing patients the majority had systemic progression. The incidence of refractory/early progressing patients in our cohort (24%) was similar to that of more intensive regimens (35%) [13]. This means that progressive patients have a dismal outcome and are unlikely to be salvaged. It is interesting to speculate whether drugs such as bendamustine, ibrutinib, checkpoint inhibitors and lenalidomide would be effective in this setting, since these drugs generally have a favorable toxicity profile, known activity in relapsed systemic B-NHL and CNS penetration [22–26].

Notably, patients who obtain a CR have an excellent outcome and probably will not benefit from additional high dose therapy, especially those patients with a low IPI at start. This challenges the role of consolidation as suggested by the French lymphoma group LYSA, that showed a positive impact of high-dose therapy followed by autologous stem cell transplantation on 3-year OS and PFS [12]. However, in our series 7 of 21 patients (33%) received consolidative radiotherapy. The indirect answer if ASCT can replace WBRT will have to come from the analysis of the IELSG32 trial, where patients with a chemosensitive PCNSL were randomized in a second randomization to WBRT or ASCT [7]. But even then we have to be cautious to extrapolate these findings to sysCNS, since PCNSL has a different biology.

Our study obviously has limitations. Firstly, its retrospective nature has inherent known and unknown biases. We have no information on the outcome of those patients with synCNS lymphoma who were considered too frail for referral to our university centers. This means that our data might be based upon a selection of those patients fit for high dosed methotrexate. Furthermore, although the rationale behind the treatment was the same, e.g. the combination of primary CNS treatment followed by systemic

immunochemotherapy, there was a considerable heterogeneity in the treatment received. Some patients were treated with a sequential MBVP/R-CHOP and others with an alternating HD-MTX/R-CHOP regimen. Although we observed no significant difference between the regimens in OS, we cannot assess the separate effect of teniposide and carmustine. In addition, 7 of 21 patients were unable to complete treatment as planned (Supplementary Figure 1). Except for gender and associated testicular or breast localization we observed no significant differences in clinical characteristics or outcome. Given its rarity, sysCNS B-NHL comparative studies can only be performed in a large, international multicentre setting. Lastly, high dose cytarabine and thiothepa were not part of the treatment regimens, although in PCNSL the addition improved outcome in a randomized phase II study [7]. Whether the addition of cytarabine or thiothepa in sysCNS B-NHL is feasible remains to be established, but might be offset by the TRM.

Conclusions

In this second largest cohort of patients with sysCNS lymphoma at presentation described to date, the outcome of patients treated with HD-MTX and R-CHOP was excellent for those patients who obtained a complete remission. This challenges the fact that these patients are excluded from most trials, and usually are considered as having a dismal prognosis. Prospective studies are needed to define the optimal treatment for these patients.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article online at <http://10.1080/10428194.2017.1285026>.

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