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Prognostic factors in 140 adult patients with non-Hodgkin's lymphoma with systemic central nervous system (CNS) involvement. A single centre analysis

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Abstract

We examined retrospectively the outcome of patients with non-Hodgkin's lymphoma (NHL) with systemic involvement of the central nervous system (CNS) registered at The Norwegian Radium Hospital (NRH) from 1980 to 1996, in order to evaluate our treatment strategy for these patients. 170 of 2561 patients (6.6%) had CNS involvement, 140 (5.5%) systemic CNS lymphoma (SCNSL) and 30 (1.2%) primary CNS lymphoma (PCNSL). Description of the patients, time of SCNSL diagnosis, symptoms at CNS diagnosis, treatment and survival were registered. The overall median survival for the 140 patients with SCNSL was 2.6 months (95% confidence interval (CI) 2.1–3.2), only 12 patients are alive in complete remission (CR). Patients with CNS involvement at diagnosis, relapse or progression during treatment for NHL had a median survival of 5.4 months (95% CI: 0.3–10.6), 3.8 months (95% CI: 0.0–9.1), and 1.8 months (95% CI: 1.0–2.7), respectively ($P=0.001$). 5 of the 8 patients consolidated with high-dose therapy (HDT) are in CR. Paresis was the only symptom that predicted survival for SCNSL. Patients above 60 years of age with CNS involvement at progression or relapse and those with paresis at the time of CNS diagnosis have a dismal prognosis. For these patients supportive therapy only should be considered. For patients under 60 years of age with chemosensitive disease, the trend was toward better prospects, and they should be offered intensive chemo-radiotherapy including HDT with autologous stem cell support.

Keywords: Non-Hodgkin's lymphoma; Adult; Central nervous system; Prognosis; Treatment

1. Introduction

Systemic central nervous system (CNS) involvement of non-Hodgkin's lymphoma (NHL) is associated with a very poor prognosis [1–5]. The early side-effects of CNS-active treatment such as high-dose methotrexate (MTX) with folinic acid rescue or radiation therapy to the total spinal axis are considerable. Leucoencephalopathy after radiation to the brain is a well known late complication [6]. Better knowledge of the variables that predict outcome might be helpful to manage the patients in different clinical situations of systemic CNS lymphoma (SCNSL).

Among 2561 patients with NHL treated during 1980–1996 at the Norwegian Radium Hospital (NRH), 170 patients (6.6%) were registered with CNS involvement; 140 (5.5%) had SCNSL and 30 (1.2%) had primary CNS lymphoma (PCNSL).

The purpose of this retrospective study was to examine the clinical course of SCNSL.

The high number of patients and long follow-up afford the opportunity to study a number of prognostic variables and CNS-related symptoms with regard to survival.

2. Patients and methods

2.1. Patients

2561 patients with NHL older than 15 years of age were diagnosed and treated at the NRH from 1980 to 1996. During this time period, the NRH has been the only hospital in the region with radiation therapy facilities. The hospital had the treatment responsibility for a population of approximately 2 million inhabitants, thus

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the patients in this study represent a largely regional population-based subset. Staging included clinical examination, chest X-ray, computed tomography (CT) scan of the abdomen, ultrasound or scintigraphic examination of the liver and spleen, bone marrow aspiration — and biopsy and standard blood tests. Clinical stage was classified according to the Ann Arbor system [7].

SCNSL is defined as NHL involvement both within and outside the CNS. The patterns of CNS involvement included meningeal, cerebral, intraspinal and epidural manifestations. Meningeal infiltration combined with other CNS localisations were in this study classified as meningeal involvement. CNS involvement was diagnosed by clinical evaluation, radiological findings on CT or magnetic resonance imaging (MRI) scan and/or cerebrospinal fluid (CSF) examination. The meninges were considered to be involved if MRI showed infiltration, and/or if the CSF showed positive cytology and/or if the white blood cell count exceeded 20×10^6/l in patients with NHL who had CNS symptoms.

A total of 170 patients were registered with CNS involvement; 140 (5.5%) with SCNSL and 30 (1.2%) with PCNSL. The patients with SCNSL had a median age of 52.5 years (range: 15–82), and the male/female ratio was 1:1. Clinical stage at the time of NHL diagnosis was as follows: stage I: 13 patients (9%), stage II: 12 patients (9%), stage III: 12 patients (9%) and stage IV: 103 patients (74%). The 30 patients (21%) with CNS involvement at diagnosis were classified as stage IV [8].

Clinical symptoms registered as potential risk factors for early death were paresis, epileptic seizure, headache, nausea/vomiting, mental change and impaired vision.

Treatment prior to and after CNS engagement was registered. Overall survival was recorded from the time of the NHL diagnosis, or from the time of the CNS diagnosis, to the last observation or death. 10 patients were treated on the basis of their CNS symptoms only; 1 at diagnosis, 1 at relapse and 8 at progression. In 2 of these cases the CNS involvement was confirmed by autopsy.

2.2. Histological groups

The histological diagnosis was established on peripheral tumour tissue and classified according to the modified Kiel classification [9]. Low-grade (L-NHL) histologies were found in 37 patients (i.e. follicular centroblastic/centrocytic, follicular and diffuse centroblastic/centrocytic, diffuse centroblastic/centrocytic, centrocytic, immunocytoma, low-grade unspecified). High-grade (H-NHL) histologies were diagnosed in 66 patients (centroblastic, anaplastic large cell, peripheral T-cell, immunoblastic, high-grade B-cell unspecified, high-grade unspecified).

27 patients with lymphoblastic or Burkitt's lymphoma were studied separately from the previously mentioned H-NHLs. In 10 cases of unspecified non-Hodgkin's lymphoma histologies, malignancy grade could not be determined. In L-NHL patients, 14/37 (38%) had a lymph node rebiopsy at the time of CNS diagnosis, and 9 of these had transformed to secondary H-NHL.

2.3. Treatment

The treatment of systemic disease followed standard protocols at the institution: patients with advanced L-NHL disease received cyclophosphamide, vincristine and prednisone (COP) until 1985, and thereafter chlorambucil and prednisone. Patients with H-NHL received eight courses of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). Lymphoblastic and Burkitt's lymphoma were treated with eight cycles of CHOP every third week, with MTX 12 mg intrathecally (i.t.) 6–8 times weekly and MTX (2 g/m^2) as a 4-h infusion in between the first six CHOP courses with folinic acid rescue after 24 h or modified LSA2-L2 from 1991. The modified LSA2-L2 regimen was given as induction chemotherapy with vincristine, doxorubicin, cyclophosphamide, L-asparaginase, prednisolone, methotrexate (i.v. and i.t.) daunorubicin, cytosine, arabinoside. Maintenance chemotherapy until a total time on all therapy 18 months with thioguanine, cyclophosphamide, hydroxyurea, doxorubicin, methotrexate, CCNU, cytosine arabinoside, vincristine and methotrexate i.t. [10]. From 1987 most of these patients who were in remission after induction chemotherapy were consolidated with high-dose therapy (HDT), total body irradiation (TBI) and autologous stem cell support. Intrathecal CNS prophylaxis was given to H-NHL patients with involvement of the bone marrow, skeleton, testis, maxillar, sphenoidal or ethmoidal sinus.

Intended therapy for patients with systemic disease with established CNS involvement generally consisted of CHOP or CHOP-like combination chemotherapy three weekly×8 with high-dose MTX (2 g/m^2)×6 with folinic acid rescue and/or i.t. MTX (12 mg×6–8) once weekly between the CHOP courses.

From 1990, patients with SCNSL less than 60 years of age who achieved a complete remission (CR) in the CNS and otherwise a CR or very good partial remission (PR) after CNS active chemotherapy and CNS-directed radiotherapy, were offered HDT with autologous stem cell support.

Patients with a local intraspinal or intracerebral infiltration received radiotherapy. One patient with epidural disease was treated with laminectomy, irradiation and chemotherapy (CHOP, MTX i.t. and intravenously (i.v.)) together with dexamethasone. Patients who did not respond to CNS-active therapy received supportive therapy until death.

2.4. Statistics

All data were registered in DataEase (DataEase International Incorporated USA 1991). Statistical analyses were performed by using SPSS for Windows (Release 8.0, SPSS Inc., Chicago, IL, USA). The Kaplan–Meier method was used for survival analysis [11], and the curves were compared by the log-rank test [12]. Multivariate analysis was performed by Cox forward regression analysis [13]. $P < 0.05$ was considered as statistically significant.

3. Results

The overall median survival from the CNS diagnosis in the lymphoma patients was 2.6 months 95% confidence interval (CI) 2.1–3.2) (Fig. 1). Only 12 patients are alive in CR. The median survival from diagnosis of NHL was 14 months (95% CI 12–16), range: 1–197.

30 patients (21%) had CNS involvement at the time of the NHL diagnosis, 27 patients (19%) at relapse and 83 patients (59%) at progression. Patients with initial CNS involvement had a median survival of 5.4 months, and the estimated 5-year survival was 20% (95% CI: 5–35%). Patients with CNS involvement at relapse had a median survival of 3.8 months, and the 5-year estimated survival was 19% (95% CI: 0.1–11%). The median survival of patients with CNS involvement at progression was only 1.8 months, and 5-year estimated survival was 5% (95% CI: 0.1–11%), ($P = 0.001$) (Fig. 2).

The median time from the diagnosis of NHL until CNS involvement at relapse was 13.6 months (range: 5.3–68.3) or until CNS progression during primary or salvage therapy 7.8 months (range: 2.2–146). The median survival from initial NHL diagnosis was 5.4 months for those with CNS involvement at diagnosis, 23 months for those at relapse and 13 months for those at progression (data not shown).

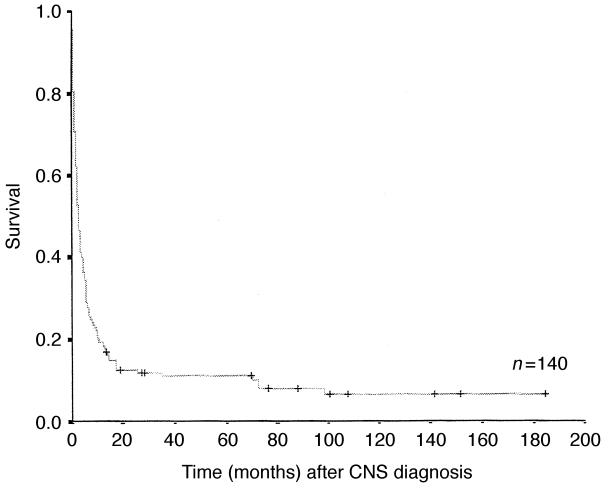

Fig. 1. Overall survival from central nervous system (CNS) diagnosis.

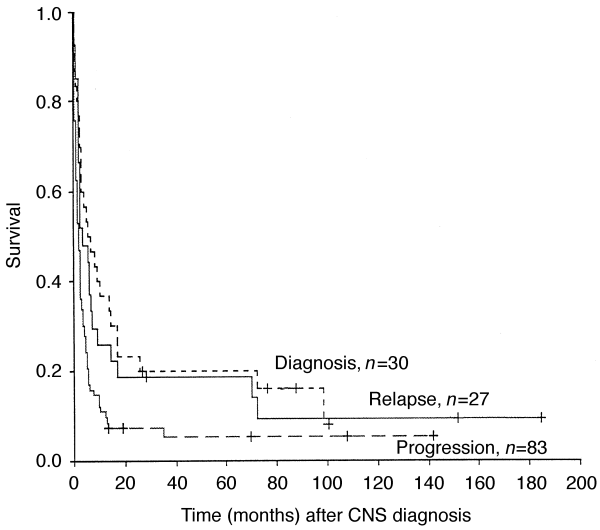

Fig. 2. Overall survival according to the time of central nervous system (CNS) involvement ($P = 0.001$).

29 patients (21%) had intracerebral involvement, 1 patient (1%) epidural involvement, 6 patients (4%) intraspinal involvement and 94 patients (67%) meningeal involvement. The localisation of CNS involvement could not be verified in 10 patients (7%). CSF was positive in 69/94 patients (73%) with meningeal involvement. The localisation of the CNS involvement had no impact on survival.

Survival did not differ significantly for patients below ($n = 97$ (69%)) or above and equal to ($n = 43$ (31%)) 60 years of age (median survival 2.8 months (95% CI: 1.8–3.8) versus 2.5 months (95% CI: 1.4–3.6)), but there was an expected trend for better survival among the younger patients (5-year survival 15% versus 1.5%, respectively) ($P = 0.08$) (Fig. 3). Known prognostic variables such as

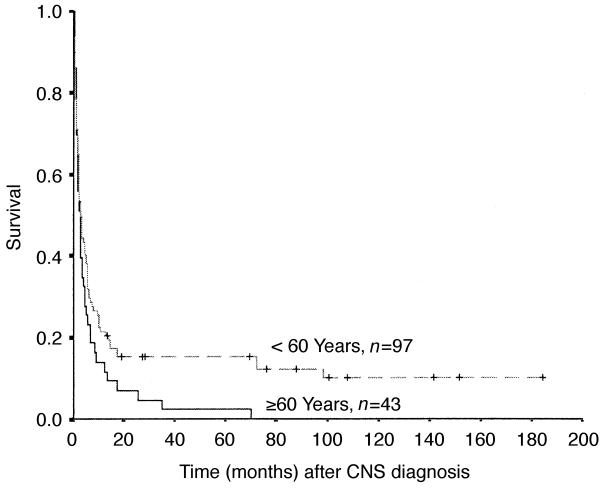

Fig. 3. Survival for patients below or above and equal to 60 years of age, ($P = 0.08$).

gender, bone marrow infiltration, serum albumin, lactate dehydrogenase (LDH) or erythrocyte sedimentation rate (ESR) had no impact on survival in patients with initial CNS involvement.

3.1. CNS-directed treatment

11 of the 30 patients (37%) with CNS involvement at diagnosis received combined CNS-directed radiotherapy and CNS-active chemotherapy. 3 patients were in CR at the last observation (2 of these 3 received HDT). 8 patients (27%) received CNS-active chemotherapy, of whom one was in CR. None of the 5 patients (17%) who received CNS-directed radiotherapy alone or those 6 (20%) who did not receive any CNS-active treatment survived.

14 of the 27 patients (52%) with CNS involvement at relapse received combined CNS-directed radiotherapy and CNS-active chemotherapy. 2 were in CR, of whom one was treated with HDT. 5 patients (19%) received CNS-active chemotherapy without radiotherapy. One of these patients is in CR at the last observation. None of the 7 patients (26%) who received only CNS-directed radiotherapy or the patient (4%) who did not receive any CNS-active treatment survived.

22 of the 83 patients (27%) with CNS involvement at progression received combined CNS-directed radiotherapy and CNS-active chemotherapy, of whom two were in CR at the last observation. Both patients also received HDT. 23 patients (28%) received CNS-active chemotherapy without radiotherapy, and 2 of these were in CR. Only 1/21 patients who received CNS-directed radiotherapy only was in CR (the patient had intracerebral involvement and was irradiated with total brain radiotherapy). The 17 patients (20%) that did not receive any CNS-active treatment did not survive. In addition to those 5 that received HDT and survived, 3 patients treated with HDT died.

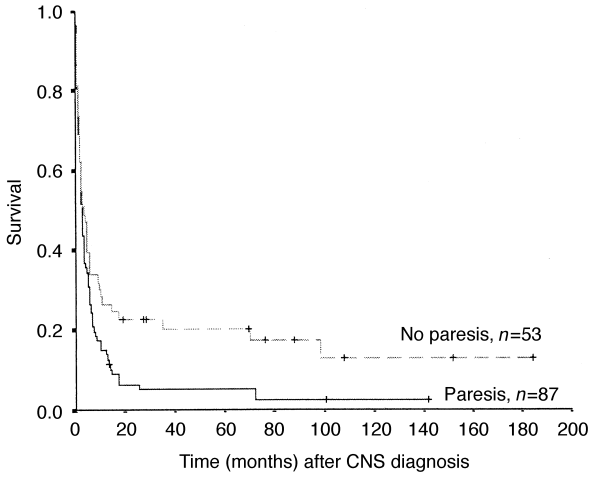

Fig. 4. Survival for patients with or without paresis ($P < 0.05$).

Of the 140 patients, 8 patients (6%) received HDT with autologous stem cell support. All of the 8 patients had meningeal involvement and achieved a CR. 3 patients relapsed and died, the remaining 5 are in a continuous CR (data not shown, Table 1). 28 of the 132 patients (21%) who did not receive HDT, achieved a CR (data not shown), of whom, 7 (25%) are in continuous CR.

The 7 patients who survived without HDT had a median age of 42 years (range: 24–58). 3 of them had localised disease (2 intracerebral and 1 intraspinal) whereas the other 4 had meningeal involvement. 6 patients received CNS-active chemotherapy (high-dose MTX intravenously (i.v.) with folinic acid rescue and/

Table 1
Description of the 8 patients who received high-dose therapy (HDT) with stem cell support

Status	Histology	Time of CNS involvement	Age (median 34.5 years range: 16–48)	Paresis	Chemotherapy at the time of CNS diagnosis (chemotherapy at NHL diagnosis)	CNS-directed radiation therapy	Bone marrow involvement
CR	Burkitt's lymphoma	Diagnosis	19	No	MmCHOP	TBI	No
CR	Lymphoblastic lymphoma	Diagnosis	26	No	MmCHOP	TBI	No
Dead of lymphoma	Lymphoblastic lymphoma	Relapse	35	Yes	Mm (LSA2-L2)	TBI	No
Dead of lymphoma	Lymphoblastic lymphoma	Diagnosis	16	No	MmCHOP	TBI	Diagnosis and relapse
CR	High-grade	Progression	37	No	Mm (MACOP-B)	TBI	Relapse
CR	High-grade	Relapse	48	No	Mm (MACOP-B)	Total CNS axis	No
CR	High-grade	Progression	34	Yes	Mm (CHOP)	Total CNS axis	No
Dead of lymphoma	High-grade	Relapse	39	Yes	Mm (CHOP)	Total CNS axis	Progression

CR, complete remission; TBI, total body irradiation; M, methotrexate (MTX) 2 g/m^2 intravenously (i.v.); m, intrathecal MTX; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CNS, central nervous system; NHL, non-Hodgkin's lymphoma; LSA2-L2, vincristine, doxorubicin, cyclophosphamide, L-asparaginase, prednisolone, methotrexate (i.v. and i.t.) daunorubicin, cytosine, arabinoside; MACOP-B, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisolone, bleomycin [19].

Table 2
Characteristics of the surviving patients

Characteristics	Patients that received high-dose therapy (HDT) with stem cell support, $n=8$ (5 in CR, 3 dead)	Surviving patients who received conventional therapy, $n=7$
Status		
CR	5	7
Dead of lymphoma	3	
Histology at NHL diagnosis		
Low-grade	0	3
High-grade	4	2
Burkitt's lymphoma/lymphoblastic lymphoma	4	0
Unspecified lymphoma	0	2
Time of CNS involvement		
At diagnosis of NHL	3 (2 CR)	2
At relapse	3 (1 CR)	2
At progression	2 (2 CR)	3
Age at NHL diagnosis (years)		
Median (range)	34.5 (16–48)	42 (24–58)
CNS-directed radiation therapy		
Total body irradiation (TBI)	5	0
Total CNS axis	3	1
Total brain	0	1
Involved (intraspinal)	0	1
No	0	4

NHL, non-Hodgkin's lymphoma; CR, complete remission; CNS, central nervous system.

or MTX 12 mg i.t.). 2 of these patients received additional radiotherapy; one for a localised intraspinal lesion, and 1 patient with meningeal involvement received radiotherapy to the total CNS axis. 1 patient with intracerebral involvement received only total brain irradiation (Table 2).

3.2. Symptoms

The CNS-related symptoms are given in Table 3. The most common symptom was paresis, present in 87 patients (62%). The estimated 5-year survival for patients without paresis was 20% compared with 5% for the patients with paresis ($P<0.05$) (Fig. 4). None of the other symptoms had an impact on survival.

Table 3
CNS-related symptoms

CNS involvement	At diagnosis $n=30$ (21%)	At relapse $n=27$ (19%)	At progression $n=83$ (59%)	Total n (%)
Epileptic seizure	0	3	8	11 (8)
Headache	8	11	39	58 (41)
Nausea/vomiting	3	10	32	45 (32)
Paresis or sensory loss	16	15	56	87 (62)
Mental change	5	11	19	35 (25)
Impaired vision	3	8	30	41 (29)

CNS, central nervous system.

3.3. Histology

Survival did not differ significantly between the histological groups when calculated from the time of the NHL diagnosis or from the time of CNS manifestation. However, when analysing patients with CNS involvement at the time of progression, the 59 patients with L-NHL ($n=25$) or H-NHL ($n=34$) had a median survival of 2.2 months, (95% CI: 1.3–3.1), and the 15 patients with lymphoblastic or Burkitt's lymphoma had a median survival of 0.95 months only (95% CI 0.5–1.4), $P=0.03$. In addition, 9 patients had unspecified NHL histology at progression. In L-NHL patients, 14/37 (38%) had a new lymph node biopsy at the time of CNS diagnosis, and 9 of these 14 (64%) had transformed to H-NHL.

3.4. Multivariate regression analysis

When entering age, paresis, histology and time of CNS involvement in a multivariate analysis, paresis (relative risk (RR) = 1.48, 95% CI 1.01–2.16, $P=0.04$) and time of CNS involvement (RR = 1.43, 95% CI 1.14–1.80, $P=0.0017$) were still significant risk factors.

4. Discussion

We describe here our experience with SCNSL treated at a regional oncology centre during a period of 17

years. This study is most likely the largest study from a single institution. Among 2561 patients, SCNSL was diagnosed in 140 cases (5.5%), which is in accordance with other studies [8,14,15]. The diagnostic procedures (i.e. the use of magnetic resonance imaging (MRI)) and treatment (i.e. the use of HDT) varied due to the long study period.

We confirm the very poor prognosis of SCNSL with an overall median survival of 2.6 months (95% CI 2.1–3.2), and with only 12/140 patients (8.6%) being in a CR at the last follow-up. This is in accordance with previous findings [1–5,16] reporting a median survival ranging from 0.5 to 5 months.

The relatively high number of patients enabled us to perform subgroup analysis and to look for prognostic variables. The time of CNS involvement had a significant impact on survival. The 5-year estimated survival was lower among patients who developed SCNS at progression (5%) compared with the time of diagnosis (20%) and relapse (19%). This is in accordance with Recht and colleagues [4], who found a median survival of 6 (range: 3–64), 5 (range: 1–23) and 2 (range: <1–8) months in the respective groups. Bashir and associates [5], and Williams and colleagues [17] also reported a better outcome for patients who had CNS involvement at diagnosis compared with those with involvement at relapse.

The majority of CNS relapses occurred within a short time after the lymphoma diagnosis, in our study after a median of 13.6 months (range: 5.3–68.3), which correlates with van Besien and associates [18] who found that almost all CNS recurrences occurred during the first year after diagnosis.

The most common symptom was paresis (62% of the patients). Other groups have shown similar findings [8,14]. In contrast, Bashir and colleagues [5] found that personality change was the most common symptom, followed by obtundation, headache, vomiting and hemiparesis. No previous study has examined whether clinical symptoms predict survival, presumably because of a lower number of patients studied.

Those 87 who presented with paresis at the time of CNS diagnosis had a 5-year survival of 5% compared with 20% for the 53 patients without paresis ($P < 0.05$). None of the other CNS symptoms had an impact on survival.

Of the 37 patients with low-grade histology, nine of 14 patients with a new lymph node biopsy at the time of CNS diagnosis had transformed to a high-grade histology. It is not known whether the persistent low-grade histology is representative for the lymphoma cells in the CNS, but it can be presumed that the lymphoma cells invading the CNS have an aggressive phenotype in the majority of the cases. Thus, the comparison between the low-grade and high-grade non-Burkitt/lymphoblastic lymphomas is of limited clinical value.

All of the 8 patients who were treated with HDT with stem cell support achieved a CR, and 5 (63%) are alive and disease-free. 28 of the 132 patients (21%) who did not receive HDT, achieved a CR (data not shown), of whom 7 (25%) are in a continuous CR. These 7 patients were younger (median 42 years; range: 24–58) than the total group (median 52.5 years; range: 15–82).

In our opinion, younger patients in CR in CNS after conventional CNS-active treatment should be considered for consolidating HDT, which also has been suggested by Williams and colleagues [17].

We suggest, based on our data, that patients below 60 years of age with SCNCL should receive intensive CNS-active chemotherapy. If a CR in CNS and a very good partial remission elsewhere is not obtained after 2–3 months of therapy, supportive treatment only should be considered. If chemosensitive disease is documented, the remission should be consolidated with radiotherapy to the CNS axis and HDT with autologous stem cell support. Patients above or equal to 60 years of age, may have a better quality of life for the short remaining lifespan with supportive therapy only.

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