Concomitant systemic and central nervous system non-Hodgkin lymphoma: the role of consolidation in terms of high dose therapy and autologous stem cell transplantation. A 60-case retrospective study from LYSA and the LOC network

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ABSTRACT

The purpose of our study is to determine the outcome of patients with systemic non-Hodgkin lymphoma presenting with neurologic localization at diagnosis, as well as the impact of consolidation in terms of high-dose therapy followed by autologous stem cell transplantation. Newly diagnosed non-Hodgkin lymphoma patients with concomitant systemic and neurological involvement at diagnosis were included in this study. Sixty patients (37 males; 25 females) were included. Median age was 61 years (23-85 years). Histological subtype was mainly diffuse large B-cell lymphoma (n=54; 90%). The International prognostic index was over 2 in 41 (72%) patients. Median number of extranodal sites was 2 (range: 1-5). Central nervous system involvement alone was documented in 48 patients. Paravertebral involvement with epidural mass and cord compression and positive cerebrospinal fluid were present in 7 patients. Five patients had both central nervous system and epidural involvement. First-line chemotherapy was mainly anthracycline-based (88%) plus high-dose methotrexate (74%) with or without cytarabine. Consolidation with high-dose therapy followed by autologous stem cell transplantation was performed in 19 patients. For the whole population, overall response rate after induction chemotherapy was 76%. Three-year progression-free survival and overall survival were 42±7% and 44±7%, respectively. For patients under 66 years of age, consolidation strategy using high-dose therapy followed by autologous stem cell transplantation positively impacted 3-year overall survival and progression free survival (P=0.008) and (P=0.003), respectively. In multivariate analysis, high-dose therapy had a positive impact on 3-year overall survival and progression-free survival for the whole population as well as for patients under 66 years old in CR after induction therapy (OS [HR=0.22 (0.07-0.67)] and progression-free survival [HR=0.17 (0.05-0.54)]). In conclusion, non-Hodgkin lymphoma prognosis with concomitant systemic and neurological involvement at diagnosis is poor with a high risk of relapse when treated with conventional chemotherapies alone. This retrospective study supports the feasibility and the potential benefit of a consolidative strategy with high-dose therapy followed by autologous stem cell transplantation in this subset of patients. This strategy and the best intensive chemotherapy regimen remain to be validated in prospective trials.

Introduction

Central nervous system (CNS) and peripheral neurological (PN) involvement at initial presentation of systemic diffuse large B-cell type lymphomas (DLBCL) represent less than 5% of systemic non-Hodgkin lymphoma (sNHL) cases.[1-4]

Although the prognosis of patients with systemic B-cell non-Hodgkin lymphoma (NHL) has improved over the last decades, these advances have not been noted across all types of NHL and varied according to the initial lymphoma sites, especially CNS localization. Systemic NHL in addition to neurological involvement remains therapeutically challenging and is associated with poor outcome. Recent retrospectives studies have highlighted the devastating prognosis of CNS involvement at relapse of sNHL with a median overall survival (OS) of seven months to 1.6 years from the time of CNS relapse.[5,6]

Little is known on the prognosis of concurrent involvement of CNS or PN at initial diagnosis of sNHL; such patients are excluded from therapeutic trials. The aim of our study is

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to report on the therapeutic characteristics of these patients as well as on the role of high-dose therapy and autologous stem cell transplantation in these settings.

Methods

Study design

Patients with histologically confirmed diagnosis of non-Hodgkin lymphoma (NHL) made between May 2002 and January 2012 with concomitant systemic and neurological involvement were retrieved from the database of the participating centers, from The Lymphoma Study Association (LYSA) database and the French network for oculocerebral lymphoma (LOC).

In accordance with the Declaration of Helsinki, approval of the University Hospital of Amiens Nord-Ouest II Ethics Committee was obtained.

Patient eligibility

Patients 18 years or older with an sNHL diagnosis with nervous system involvement were eligible for this study. Diagnosis of NHL was made according to international diagnostic criteria used at the time of diagnosis. Diagnosis of systemic lymphoma was done on lymph nodes or using tissue biopsies. Nervous system involvement was defined by brain parenchyma, intra-ocular, cranial nerve, or meningeal involvement, as well as paravertebral mass and CSF involvement with lymphoma cells. Diagnosis was based on positive cerebrospinal fluid (CSF) cytology or immunophenotyping or by biopsy-proven parenchymal brain localization. Patients with CNS localization based on a typical CT-scan and/or magnetic resonance imaging (MRI) and concurrent sNHL were included as well.

Treatment and assessments

At base-line assessments of patients and disease included ECOG score, Ann Arbor stage, international prognostic index (IPI), lactate dehydrogenase (LDH) level, bone marrow histology, CSF cytological and/or flow cytometry analysis, CT-scan of the thorax, abdomen and pelvis. Cerebral and vertebral CT-scan and/or MRI were also recorded.

Table 1. Patients' characteristics at diagnosis.

	Total (n=60)	High dose therapy (n=19)	Chemotherapy alone (n=41)	P
Median age; (range, years)	61 (23-85)	54 (23-67)	66 (23-85)	
Patient Age; n (%)				
< 60	28 (47)	14 (74)	14 (34)	0.006
≥ 60	32 (53)	5 (26)	27 (66)	
Gender; n (%)				
Male	35 (58)	12 (63)	23 (56)	0.779
Female	25 (42)	7 (37)	18 (44)	
Histology; n (%)				
DLBCL	54 (90)	18 (95)	36 (88)	0.654
Others	6 (10)	1* (5)	5** (12)	
IPI; n (%)				
0-2	16 (28)	10 (53)	6 (15)	0.003
3-5	41 (72)	8 (42)	33 (78)	
Missing data	3 (6)	1 (5)	2 (7)	
LDH; n (%)				
normal	23 (40)	7 (37)	16 (39)	1
elevated	35 (60)	11 (58)	24 (59)	
missing	2 (4)	1 (5)	1 (2)	
ECOG score; n (%)				
0	28 (48)	11 (58)	17 (41)	0.258
≥ 1	30 (52)	7 (37)	23 (57)	
missing	2 (3)	1 (5)	1 (2)	
&Number of extranodal sites; n (%)				
1	15 (25)	7 (3)	8 (20)	0.202
≥ 2	45 (75)	12 (63)	33 (80)	
Nervous system involvement; n (%)				
Central alone+	48	18	30	0.736
Epidural alone ++	7	0	7	
Both	5	1	4	
Bone marrow involvement; n (%)				
yes	25 (45)	8 (42)	21 (52)	0.569
no	31 (55)	10 (53)	17 (41)	
not done	4 (6)	1 (5)	3 (7)	

*DLBCL: diffuse large B cell lymphoma; IPI: international prognostic index; LDH: lactate dehydrogenase: ECOG: Eastern Cooperative Oncology Group. *Anaplastic large cell lymphoma ALK+ (n=1). **Peripheral T-cell lymphoma NOS (n=2), mantle cell lymphoma (n=2). &. extra nodal sites included, bone marrow, bones, spleen, liver, breast, testis, adrenal glands, ovaries, gastro-intestinal tract, lungs and parotid gland; + intraventricular, parenchymal, meningeal, cranial nerve; ++ paravertebral lesions with epidural mass and cord compression with CSF involvement.*

The type of chemotherapy administered, total dose of drugs per cycle and the use of high-dose therapy as well as radiotherapy were retrieved from the original patient files.

Response assessment was performed by the on-site referent physician according to the International Working Group Criteria (IWC) for sNHL and the International Primary CNS Lymphoma Collaborative Group for CNS disease.[7,8]

Statistical analysis

Quantitative variables were expressed as mean±standard deviation or as median [range] and qualitative variables as percentages. The Student or Wilcoxon test was used for comparison of quantitative variables between two groups. χ^2 or Fisher's test were used to compare categorical variables. Overall survival (OS) was defined as the time between diagnosis and the date of death or last follow up. Univariate standard and time-varying (for intensive therapy) Cox models were used to assess prognostic factors for OS and to compute hazard ratios (HRs) and their 95% confidence interval (95%CI).

Variables eligible for the multivariate time-varying Cox model were those variables with $P<0.10$ in univariate analysis.

Survival distributions were estimated using the adjusted Kaplan-Meier method. P-values were two sided and $P<0.05$ were considered significant in multivariate analysis. SAS software v. 9.2® (SAS Institute, Cary, NC, USA) was used for all analysis.

Results

Patients' characteristics

Eighty-three patients were initially identified in our databases (Table 1). Twenty-three patients were excluded from the analysis on account of missing data or uncertain diagnosis (n=14), for Burkitt's lymphoma diagnosis (n=4) or unspecified small B-cell lymphoma (n=2) or follicular lymphoma (n=3). A total of 35 male and 25 female patients with a median age of 61 (range 23-85 years) years at lymphoma diagnosis were analyzed.

Histopathological subtypes were predominantly diffuse large B-cell (DLBCL) (n=54; 90%). Other histology included mantle cell lymphoma (n=2), peripheral T-cell lymphoma (n=2) and anaplastic large cell lymphoma ALK+ (n=1) and unclassified high-grade lymphoma (n=1). Histological diagnosis was made on lymph nodes (n=42), CNS (n=1), paravertebral mass (n=12), and other extra nodal tissue (n=5) biopsies.

In DLBCL cases, the IPI was high in 72% of cases and

Table 2. First-line treatments and responses.

[a]Treatment	Total n=60	CR n=41 (68%)	PR n=5 (8%)	Progression n=10 (17%)	NE n=4 (7%)
	First-line treatment				
Systemic chemotherapy					
Anthracycline based; n (%)	52 (87)	36 (60)	5 (8)	7 (12)	4 (7)
CHOP (-like) alone	8	3	1	4	0
CHOP + HD MTX	5	4	1	0	0
ACVBP	5	4	0	1	0
COPADEM	3	2	0	0	1
CHOP (-like)+ HD MTX and HD araC	31	23	3	2	3
HD Methotrexate-based without anthracyclines; n (%)	6 (10)	5 (8)	0	2 (2)	0
alone	2	2	0	1	0
+ HD araC	4	3	0	1	0
Others	2 (3)	0	0	2 (3)	0
Intravenous rituximab; n (%)					
yes	56 (93)	40 (67)	5 (8)	7 (12)	4 (6)
no	4 (7)	1 (2)	0	3 (5)	0
*Radiotherapy ; n (%)					
yes	4 (7)	4 (7)	0	0	0
no	56 (93)	37 (62)	5 (8)	10 (16)	4 (7)
**Intrathecal chemotherapy, n (%)					
yes	43 (72)	31 (52)	4 (7)	6 (10)	2 (3)
missing	17 (28)	10 (16)	1 (2)	4 (7)	2 (3)
	Consolidation treatment with high-dose therapy + ASCT				
ASCT, n (%)					
yes	19 (32)	19 (32)			
no	41 (68)	22 (37)	5 (8)	10 (16)	4 (7)

*CR: complete remission; PR: partial remission; NE: non evaluable for toxic death; CHOP: cyclophosphamide, doxorubicine, vincristine, prednisone, HD: high dose; MTX: methotrexate (median dose 3 g/m²); ACVBP: adriamicine, cyclophosphamide, vinblastine, bleomicine, prednisone (4 cycles followed by HD MTX (2 cycles) and ifosfamide and aracytine; COPADEM: cyclophosphamide, oncovin, prednisone, adriamicine, HD MTX, Ara-C: aracytine; ASCT: autologous stem cell transplantation. [a]Efficacy of treatment (CR, PR, or progression were evaluated after the end of chemotherapy and before high-dose therapy if applicable). *Three patients received whole cranial irradiation and 1 patient received radiotherapy at the vertebro- meningeal lesions. ** Methotrexate alone (n=8); Methotrexate+ AraC (n=8), Liposomal AraC (n=6), Methotrexate+AraC+ Liposomal AraC (n=15), AraC (n=1), Methotrexate+ Liposomal AraC (n=1).*

LDH level was above normal value in 60% of cases. Extra nodal disease was present at 2 or more sites in 75% of patients and bone marrow involvement was detected in 45%.

Central nervous system involvement such as parenchymal, intraventricular, meningeal or cranial nerve was documented in 48 patients. Seven patients had paravertebral involvement with an epidural mass, cord compression and CSF involvement by lymphoma cells and 5 patients had both CNS and paravertebral nervous system lesions. Forty-three patients had data regarding CSF involvement. Thirteen patients had CSF involvement with lymphoma whereas 30 patients did not. No patients had a diagnosis of intra-ocular lymphoma.

As expected, patients over 60 years of age received less high dose therapy (*P*=0.006).

Treatment

Induction chemotherapy: anthracycline-based chemotherapy was used in the majority of patients (n=53; 87%), either. alone (n=8, 13%) or in combination with high-dose methotrexate (HD-MTX) [R-CHOP-MTX (n=5). R-ACVBP (n=4); others (n=3)] or with HD-MTX plus high-dose aracytine (HD-araC) (n=31). HD-MTX–based chemotherapy without anthracyclines was administered along with HD-araC in 4 patients (Table 2). Two patients received MTX-based chemotherapy alone; 2 patients received palliative therapy. A total of 58 patients (97%) received a CNS-targeted chemotherapy.

In the majority of patients, rituximab immunotherapy was used in combination with chemotherapy (n=57; 95%). Three patients did not receive rituximab because of T-cell lymphoma. Intrathecal chemotherapy (IC) was added in 39 patients. Three patients received whole cranial irradiation and one patient received 30 grays radiotherapy at the vertebro-meningeal lesions.

High-dose therapy and autologous stem cell transplant: IC + ASCT was performed in 19 (32%) patients (DLBCL=18, ALCL=1) as a consolidation therapy in first remission. Median patient age was 54 (range 23-67) years (only 1 patient >65 years). Median time from diagnosis to ASCT was 6.1 (3.3-14.5) months. Reasons for not receiving IC + ASCT were: progressive disease (n=10), age >65 years (n=15), premature toxic death (n=4), and physician decision (n=12). In patients under 65 years of age, reasons for not receiving IC + ASCT were progressive disease (n=5), toxic death (n=3), and physician decision (n=12).

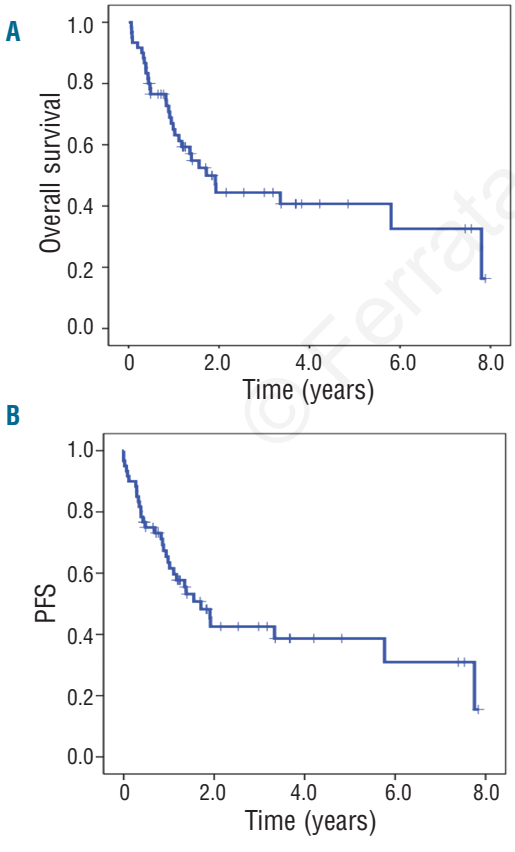

Figure 1. (A) 3-year overall survival (OS) (44 ± 7%) for the whole population; (B) 3-year progression-free survival (PFS) (42 + 7 %) for the whole population.

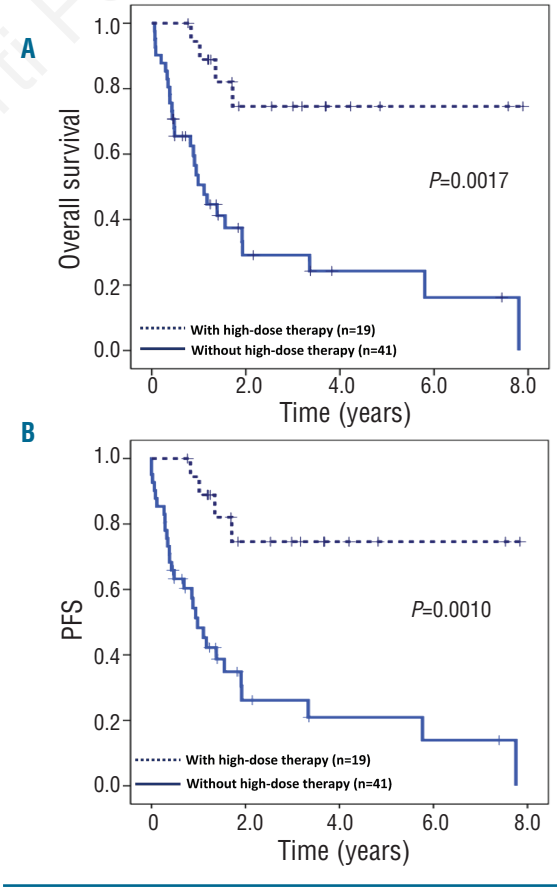

Figure 2. (A) 3-year overall survival (OS) (75% *vs.* 29%) for the whole population according to IC + autologous stem cell transplantation (ASCT) as a consolidative therapy; (B) 3-year progression-free survival (PFS) (75% *vs.* 26%) for the whole population according to IC + as a consolidative therapy.

High-dose therapy consisted of BEAM (carmustine 300 mg/m²; day -6, etoposide 200 mg/m²; day -5 to -2, cytarabine 400 mg/m²; day -5 to -2, melphalan 140 mg/m² day -1) regimen (n=8), TBC (thiotepa 250 mg/m² day -9 to -7, busulfan 0.8 mg/kg every 6 hours day -6 to -4 (10 doses if ≤ 60 years and 8 doses if > 60 years) and cyclophosphamide 60 mg/kg day -3 to -2) regimen (n=8), total body irradiation, cyclophosphamide, etoposide (n =2) and cyclophosphamide, carmustine, etoposide and novantrone (n =1).

Among patients who received IC + ASCT, a higher proportion of patients were under 60 years of age and presented more frequently an IPI below 3 at diagnosis as compared to patients who received conventional chemotherapy alone (Table 1). Other characteristics such as gender, ECOG score, LDH level, number of extranodal sites, pattern of nervous system involvement, and bone marrow infiltration were similar between the two patient groups.

Outcome: after induction chemotherapy, ORR was 76% with complete remission (CR) in 41 (68%) and partial remission in 5 (8%) patients. Ten patients had progressive disease during chemotherapy and 4 patients died during chemotherapy from treatment-related toxicity (severe sepsis=2; septic shock=3) and thus not evaluable for response. For patients who were in first CR, 19 received consolidative therapy with IC+ASCT and 22 patients did not. For the whole group of patients, 3-year overall survival (OS) and progression free survival (PFS) were 44 + 7% and 42 + 7%, respectively.

Eighteen patients relapsed after a median duration of response of 4.9 (range 0.7-66) months. Five patients relapsed after ASCT and 13 patients after chemotherapy alone (from CR=12 or PR=1) with a median time duration of relapse of 9.8 (2-66) and 4.8 (0.7-34) months, respectively.

After a median follow up of 14.7 (range 0.1 - 97) months from the diagnosis date, 32 patients died from lymphoma (n=25) and sepsis (n=7). Twenty-eight patients remained alive in CR (n=26) or PR (n=2).

Prognostic factors

For the whole group of patients: in univariate analysis, 3-year OS was positively influenced by IC + ASCT (75% *vs.* 29%; *P*=0.0017). IC + ASCT had also a positive impact on 3-year PFS (75% *vs.* 26%; P=0.001) (Figure 2 and *Online Supplementary Table S1*).

In multivariate analysis, 3-year OS and PFS were positively and significantly impacted by IC+ASCT: [*P*=0.003; HR=0.20 (0.07-0.59)] and [*P*=0.001; HR=0.17 (0.06-0.49)], respectively (*Online Supplementary Table S2*).

For patients under 65 years of age: thirty-eight patients were in first CR after induction chemotherapy. Eighteen received IC + ASCT and 20 patients did not. We compared the outcomes of the two groups.

In univariate analysis, 3-year OS and PFS were positively influenced by IC + ASCT 73% *vs.* 28% (*P*=0.0008) and 73% *vs.* 21% (*P*=0.003), respectively (Table 3; Figure 3).

In multivariate analysis, high-dose therapy remained the only significant parameter that positively affected OS [*P*=0.008; HR=0.22 (0.07-0.67)] and 3-year PFS [*P*=0.002; HR=0.17 (0.05-0.54)] (Table 4).

Eight patients received TBC as conditioning regimen and 8 others received BEAM regimen. There was no difference between the 2 regimens regarding relapse rate and death.

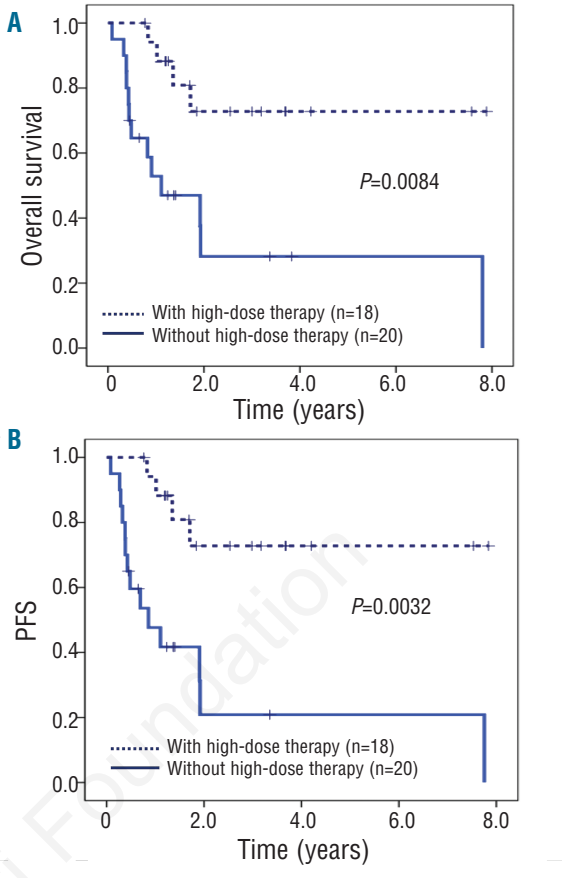

Figure 3. (A) 3-year overall survival (OS) (73% *vs.* 28%) of patients ≤ 65 years and in first complete remission according to IC + ASCT; (B) 3-year progression-free survival (PFS) (73% *vs.* 21%) of patients ≤ 65 years and in first complete remission according to IC + ASCT.

Discussion

The worse prognosis of secondary CNS lymphoma defined by CNS involvement at any time during the course of sNHL, has been widely recognized when patients are treated with conventional chemotherapies. The rarity of this form of lymphoma, excluded from therapeutic trials, explains the lack of clear therapeutic guidelines for these patients. We have reported a homogeneous series of adult patients with NHL presenting at diagnosis with concomitant systemic and neurological involvement. Our population exhibits a high percentage of patients with elevated IPI and LDH level, and involvement of more than 2 extranodal sites, which are recognized as risk factors for CNS involvement by the lymphoma.[2,9,10]

The benefit of a consolidative strategy using IC + ASCT in the case of CNS relapse in sNHL has been previously suggested by retrospective studies from the European Group for Blood and Marrow Transplant (EBMT), the International Primary CNS Lymphoma Collaborative Group (IPCG), as well as retrospective, single center studies. This study provided sNHL data mainly at relapse.[5,6,11-14]

The benefit of such a strategy has not yet been shown in the specific setting of concomitant neurological and systemic NHL at diagnosis. Most of the published series included patients with CNS disease at diagnosis or at relapse. Due to the retrospective nature of the study, the small sample size and the absence of data on the choice of the treatment strategy, selection bias may have influenced patients' outcome. In this study, which included exclusively patients who presented with systemic and neurological lymphoma, the use of IC + ASCT in patients in CR confers a survival advantage compared to conventional chemotherapies without consolidation treatment.

In a study from the CIBMTR, Maziarz *et al*. reported on 151 adult patients with sNHL and CNS involvement at any time prior to ASCT. The authors confirm an excellent long-term outcome of patients who were transplanted in CNS remission at the time of transplant.[9]

Our results in the subgroup of patients who received IC + ASCT compare favorably with those of Maziarz who reported a 3-year OS and PFS of 58% and 46% in patients in CNS remission at time of ASCT. However, our patients were treated in the front-line setting, whereas, in the study by Maziarz *et al*., 125 (83%) patients received 2 or more lines of chemotherapy prior to ASCT. Our results are in accordance with those from Dana Farber Cancer Institute and Massachussets General Hospital.[15] The authors reported on 16 patients with secondary CNS lymphoma, including 9 patients with CNS involvement at time or within six months of diagnosis of the sNHL. Excellent outcomes were reported; with a short median follow up of 379 days, 1-year OS and PFS were 88% and 80%, respectively.

Table 3. Univariate analysis by key subsets: 3-year overall and progression-free survival rates and *P* values for patients 65 years or under.

	N. of patients	Overall survival			Progression-free survival		
		%	HR [95%CI]	*P**	%	HR [95%CI]	*P**
Gender				0.11			0.04
Male	22	61	1		61	1	
Female	16	34	2.26[0.83-6.13]		26	2.78 [1.04-7.54]	
IPI				0.23			0.48
0-2	14	70	1		63	1	
3-5	22	38	2.01 (0.64-6.32)		38	1.46 [0.51-4.22]	
LDH				0.59			0.50
normal	15	34	1		54	1	
elevated	22	59	1.70 (0.64-4.55)		34	1.39 [0.53-3.57]	
ECOG				0.94			0.83
0	21	53	1		48	1	
≥ 1	15	46	1.04 (0.39-2.80)		46	1.11 [0.42-2.94]	
Number extranodal sites				0.40			0.29
0	10	80	1		80	1	
≥ 1	28	42	1.71 (0.49-6.20)		36	1.95 [0.56-6.80]	
Bone marrow involvement				0.30			0.47
no	14	56	1		51	1	
yes	22	36	1.73 (0.62-4.87)		36	1.45 [0.53-3.95]	
High-dose therapy				0.008			0.003
yes	18	73	1		73	5.40 [1.76-16.67]	
no	20	28	4.57 [1.48-14.08]		21		

HR: hazard ratio; CI: confidence interval; IPI: international prognostic index; LDH: lactate dehydrogenase; ECOG: Eastern Cooperative Oncology Group.The effect of high dose therapy on overall survival and progression-free survival was studied with a Cox model with time varying covariate to avoid time varying bias.

Table 4. Multivariate analyses for patients 65 years or under.

Characteristics	Overall survival			Progression-free survival		
	HR	95% CI	*P**	HR	95% CI	*P**
High-dose therapy						
No		1			1	
Yes	0.22	0.07-0.67	0.008	0.17	0.05-0.54	0.002
Gender						
Male					1	
Female				3.15	1.10 – 9.00	0.032

HR: hazard ratio; CI: confidence interval; IPI: international prognostic index.

The importance of obtaining complete remission especially of CNS lesions, before ASCT, has been recurrently showed. The use of HD-MTX before IC + ASCT was associated with a better PFS in one preliminary study,[16] whereas prior CNS radiotherapy has not be associated with a better survival after ASCT.[12] Few or no patients with concomitant CNS and sNHL at diagnosis are reported in these studies, and, except for the more recent one,[15] very few patients had received HD-MTX +/- HD Ara-C, which can be considered as the best CNS-targeted therapy according to therapeutic results in primary CNS lymphomas.[17] In our series, 80% of patients received HD-MTX as part of first-line therapy and rituximab was administered also in nearly all patients.

Multiple types of intensive chemotherapies have been used in our series as well as in the majority of published series, precluding any strong recommendations regarding the best high-dose therapy regimen. BEAM regimen, mostly used in sNHL, and thiotepa-based regimens, mostly used in primary CNS lymphoma (PCNSL), have been reported along with TBI or busulfan-based regimens. Thiotepa, busulfan, cyclophosphamide (TBC) regimen has demonstrated excellent activity in relapse PCNSL[18] as well as in first-line PCNSL or in sCNSL.[15] Other Thiotepa-based high-dose therapy associated with carmustine have been proved effective in first-line treatment of PCNSL.[19] Encouraging preliminary results have been reported by Street *et al.*[20] in patients treated for CNS involvement at diagnosis or at relapse of an sNHL, with a high-dose therapy consisting of either TBC or rituximab-thiotepa-busulfan-melphalan. The 2-year PFS and OS were 61% and 68%, respectively. The combination of thiotepa-carmustine and etoposide has been used in a prospective study including 30 patients with CNS relapse of sNHL.[21] The CR rate rose from 26% (7 patients) after induction therapy to 63% (15 of 24 patients) after IC + ASCT, and led to a 2-year OS of 63%, nevertheless there were only 7 patients out of 24 in CR before ASCT. Results of BEAM conditioning regimen have been less studied in the case of CNS involvement by NHL. One study[22] evaluated this regimen in first CR of newly diagnosed PCNSL with disappointing results. In other studies, brain irradiation was systematically used after BEAM + ASCT, thus making the role of ASCT difficult to assess.[23,24] In sCNSL, BEAM and similar regimen has been used in 70 patients (46%) and TBI-based conditioning regimen in 35 patients (23%) by Marziaz *et al.*[9] A prospective study was conducted by the HOVON group for patients in CNS relapse of an sNHL and treated with R-DHAP MTX followed by IC consisting of busulfan and cyclophosphamide. Results were disappointing with a median PFS of only six months.[25]

In our series, 8 patients received thiotepa, busulfan and cyclophosphamide (TBC) regimen and 8 others received BEAM regimen. There was no difference between the 2 regimens regarding relapse rate and mortality. However, the small number of patients precludes any firm conclusion. Thus, we could consider, based on these results, despite the fact that only prospective randomized trials could answer this question, the combination of rituximab plus CHOP or CHOP-like chemotherapy in combination with HD-MTX +/- HD Ara-C, as the preferable first-line treatment for patients with systemic and CNS NHL, followed in cases of complete remission, by an IC+ HCT. Although thiotepa-based conditioning has been more widely used in this patient setting, further study needs to be conducted on the best combination for the high-dose therapy.

Authorship and Disclosures

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