Secondary infiltration of the central nervous system in patients with diffuse large B-cell lymphoma

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Objective: *To investigate the incidence and risk factors of infiltration of the central nervous system after the initial treatment of diffuse large B-cell lymphoma in patients treated at Santa Casa de Misericórdia de São Paulo.*

Methods: *A total of 133 patients treated for diffuse large B-cell lymphoma from January 2001 to April 2008 were retrospectively analyzed in respect to the incidence and risk factors of secondary central nervous system involvement of lymphoma. Intrathecal prophylaxis was not a standard procedure for patients considered to be at risk. This analysis includes patients whether they received rituximab as first-line treatment or not.*

Results: *Nine of 133 (6.7%) patients developed central nervous system disease after a mean observation time of 29 months. The median time to relapse or progression was 7.9 months after diagnosis and all but one patient died despite the treatment administered. Twenty-six (19.5%) patients of this cohort received rituximab as first-line treatment and nine (7.1%) received intrathecal chemoprophylaxis. Of the nine patients that relapsed, seven (77.7%) had parenchymal central nervous system involvement; seven (77.7%) had stage III or IV disease; one (11.1%) had bone marrow involvement; two (22.2%) had received intrathecal chemoprophylaxis; and 3 (33.3%) had taken rituximab. In a multivariate analysis, the risk factors for this infiltration were being male, previous use of intrathecal chemotherapy and patients that were refractory to initial treatment.*

Conclusion: *Central nervous system infiltration in this cohort is similar to that of previous reports in the literature. As this was a small cohort with a rare event, only three risk factors were important for this infiltration*

Keywords: *Lymphoma, large B-cell, diffuse; Central nervous system neoplasms/secondary; Doxorubicin/administration & dosage; Drug administration schedule; Antineoplastic Agents/therapeutic use; Multivariate analysis; Risk factors*

Introduction

Infiltration of the central nervous system (CNS) by diffuse large B-cell lymphoma (DLBCL) is a subject of great interest because it presents concepts that are still controversial, the treatment is aggressive and it has a reserved prognosis. The risk factors for CNS infiltration have been analyzed in various case series, the majority of which have sought to evaluate, through univariate and multivariate analysis, the known, previously reported, risk factors of aggressive and very aggressive lymphomas[1-3].

The incidence of CNS infiltration of DLBCL varies from 1.1 to 10.4%[3-12] and occurs, in the majority of cases, during the course of chemotherapy or in the first 36 months of follow-up. A decrease in incidence has already been demonstrated with the use of systemic rituximab, probably because it presents a response pattern with a higher rate of complete remission[10].

The main risk factor for infiltration of the CNS by lymphoma is the histological subtype[12]. Burkitt's and T-lymphoblastic lymphomas have infiltration rates of 17-47%[13-18]. Meanwhile, the risk of infiltration in slow-growing lymphomas is very low[13,14]. Besides the histological subtype, the main risk factors for infiltration are an increase in lactate dehydrogenase (LDH) and the presence of more than one extranodal site affected by the lymphoma[2]. Other articles report a higher incidence when the lymphoma is located in the paranasal sinuses[14,19], testicles[14,19,20] bone marrow[21], orbit[14], breasts[21,22] and epidural lesions[19,23,24]. Advanced stage has also been reported as a risk factor for infiltration[13,15,16,25].

In DLBCL in particular, there are few reports of large case series analyzing the relevant risk factors for CNS infiltration. In the current state of knowledge, it is necessary to investigate the risk factors thoroughly, particularly in patients undergoing chemotherapy associated with rituximab, to identify patients at high risk, among whom a more in-depth investigation of probable asymptomatic infiltration of the CNS is necessary.

Methods

This retrospective study was undertaken in Santa Casa de Misericórdia de São Paulo based on a review of the medical records of patients who were consecutively diagnosed as having DLBCL and were followed up in the service between January 2001 and April 2008. The

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The authors declare no competing financial interest

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research was approved by the local Ethics Committee. Informed consent was waived due to the retrospective design.

The monoclonal antibody rituximab was systematically incorporated in the treatment of all patients with DLBCL only in September 2007. Before that, our patients took the cyclophosphamide, doxorubicin, vincristine and prednisone regimen (CHOP).

The event being analyzed here was CNS infiltration. The period for the infiltration was defined from diagnosis to confirmation by cerebrospinal fluid (CSF) or imaging exams. Besides CNS infiltration, the treatment administered, the response to treatment and the survival period after infiltration, determined from the time of infiltration to death or loss to follow-up, were assessed. These data were collected from the registries of the Pathological Analysis Department of the institution and from the medical records of the hospital. Other variables were also evaluated: age, diagnosis date, disease site, presence of bulky disease (defined as a mass larger than 10 cm), stage, International Prognostic Index (IPI), bone marrow involvement, serum LDH, blood count at the time of diagnosis, albumin, beta-2 microglobulin, erythrocyte sedimentation rate (ESR), uric acid, serum human immunodeficiency virus (HIV) positivity, use of rituximab, intrathecal prophylactic chemotherapy (IPC), recurrence, date of death, and date of loss to follow-up. There was no data regarding the immunophenotyping of the lymphoma cell.

The overall survival was evaluated from the diagnosis to the last follow up/contact with the patient or patient death. The overall survival analysis was performed with the aim of comparing it with populations of other studies with the same primary objective or similar cohorts.

IPC was used in few patients, and always associated to the first four cycles of treatment (Range: 2-4 cycles).

B symptoms were defined as the presence of at least one of the following: night sweats, weight loss of more than 10% of the body weight in six months and fever (not infectious).

Patients

During the study period, 138 patients were diagnosed with DLBCL according to the 2008 World Health Organization (WHO) criteria[26]. The diagnosis was confirmed by two pathologists (RPP and IC) from the institution. Patients with the diagnosis of DLBCL that evolved from low-grade lymphoma were excluded. Five primary CNS lymphoma cases were also excluded. Patients positive for HIV were not excluded.

The data of the remaining 133 patients were analyzed. The response to treatment was determined based on lab exams (LDH, ESR, beta-2 microglobulin) and on thorax, abdomen and pelvis computed tomography (CT) results, according to the criteria by Cheson et al.[27]. A biopsy was performed for all patients who had bone marrow involvement at the time of diagnosis. A complete response was confirmed only when the biopsy was negative at the end of treatment.

Diagnosis of secondary CNS infiltration, made by CSF cytology and head CT and/or head and spine magnetic resonance imaging (MRI), were used in case of clinical suspicion of infiltration. Only one case of secondary infiltration was confirmed by histology.

Statistical analysis

Univariate analysis was performed based on the estimated relative risk with 95% confidence interval (CI) and p-value to assess the possible risk factors for this infiltration. The age at diagnosis, gender, site of onset of illness, presence of two or more sites of extranodal disease, presence of bulky disease, disease stage (I/II or III/IV), presence of B symptoms, IPI (< 3 or ≥ 3), bone marrow biopsy (positive or negative), LDH (normal or increased), hemoglobin at diagnosis, albumin (< 4 and ≥ 4), dosage of beta-2-microglobulin (normal or high) prophylactic intrathecal chemotherapy (yes or no), type of treatment given, response to initial treatment and evaluation of the outcome of death were evaluated. Among these variables, a previous analysis was made to verify common differences between the patients who had CNS infiltration or not. The Mann-Whitney test was used for the comparison between groups with and without CNS infiltration according to socio-economic variables, clinical data and treatments. The Fisher exact test was used for discrete variables.

When comparing the survival curves in respect to infiltration of the CNS as the outcome to determine the ratio of incidence rates of the event infiltration, some risk factors were presented with statistically significant incidence rates. In the context of this univariate analysis, the following variables were evaluated: age at diagnosis (< 60 or ≥ 60 years), gender, number of extranodal sites (< 2 or ≥ 2), presence of bulky disease, disease stage (I/II or III/IV), presence of B symptoms, IPI (0-2 vs. 3-5), involvement of the bone marrow, LDH (normal or increased), hemoglobin (Hb - < 10.5 mg/dL or ≥ 10.5 mg/dL), albumin (< 4 or ≥ 4), increased beta-2 microglobulin, treatment performed (chemotherapy vs. chemotherapy + radiotherapy vs. others), response pattern (complete remission vs. partial remission vs. refractory). In this context, the final outcome of death was also evaluated.

Survival curves by the Kaplan and Meier method were constructed for both the outcome of death and for the outcome of CNS infiltration. The Cox regression model was used in the multivariate analysis to establish the factors that are associated with overall survival curve in the two outcomes. The log-rank test was used to compare the different levels of significant factors. The incidence rate was estimated by the incidence density, considering the follow-up period of 103 months. In all the comparisons, probabilities were considered significant when tests values (p-value) were less than 0.05.

Results

Characteristics of the study population

The epidemiological, clinical and laboratory findings of the study population are shown in Table 1. The median follow-up was 29.1 months. Among the 133 patients, 74 (55.6%) were male. The average age was 52.4 years and median age was 52.7 years. Seventy-two of the 133 patients (54.2%) were in Stage III and IV at diagnosis and 48/131 (36.7%) had IPI ≥ 3.

With respect to the initial location of the lymphoma, 71.4% had nodal disease only and of these, 8.3% had retroperitoneal

Table 1 - Characteristics of patients with diffuse large B-cell lymphoma in the Santa Casa cohort followed from 2001 to 2008

	Average	Range
Age (years)	52.4	16-85
	n	**%**
Gender		
Male	74	55.6
Female	59	44.4
Stage		
I-II	61	45.9
III-IV	72	54.1
Presence of bulky disease*	33	24.8
Presence of B symptoms**	82	61.7
International Prognostic Index		
0-2	83	63.4
3-5	48	36.7
Bone marrow involvement	13	10.0
Increased lactic dehydrogenase (U/L)	98	74.8
Number of extranodal sites involved		
0-1	123	92.5
≥ 2	10	7.5
Prophylactic intrathecal chemotherapy		
Yes	9	7.1
No	118	92.9
Response to treatment		
Complete	75	59.5
Partial	18	14.3
Refractory	33	26.2

*Bulky: mass size > 10 cm; ** B symptoms: night fever, night sweats and fever

involvement, not necessarily with a bulky mass, 17.3% had a mediastinal mass, 2.3% had paranasal sinus involvement, 2.3% had the initial presentation of disease in the paravertebral region and two patients had testicular disease. Only 7.5% of patients had more than two extranodal sites involved.

Bulky disease was seen in 33/133 (24.8%) of patients. B symptoms were reported in 82/133 (61.7%) cases.

Lab results were as follows: LDH was high in 98/131 (74.8%) cases, with an average of 660.5 U/L and a median of 425 U/L (reference values in the institution are < 278 U/L). Forty-five of 104 (43.3%) patients had albumin below 4 g/dL and 19/55 (34.5%) had increased beta-2 microglobulin (> 2.7 mg/L) not correlated with renal function or seropositivity for HIV. As mentioned above, 4/131 (3.1%) patients had serology for HIV confirmed as positive and these patients were not excluded.

The unilateral bone marrow biopsy was documented in 130 patients and of these, 13 (10%) presented involvement by lymphoma.

Ninety-seven of 127 (76.4%) patients underwent only chemotherapy as first-line treatment, 25/127 (19.7%) underwent combined treatment of chemotherapy plus radiotherapy and 5/127 (3.9%) underwent other treatments.

During the study period, as there was no defined protocol for IPC, the characteristics of the patients that received it were variable and not based on risk factors for CNS infiltration. There was information about it in the medical records of 127 patients; in 9 of these IPC was performed (7.15%). The anti-CD20 monoclonal antibody rituximab was used in 26/133 (19.5%) patients. This medication was incorporated into first-line treatment in September 2007. The response was complete in 59.52% of the patients, 18/126 (14.3%) achieved partial response and 33/126 (26.2%) were refractory to initial treatment.

Characteristics of patients with central nervous system infiltration

CNS infiltration occurred in 9/133 patients, with an incidence of 6.7% of patients and incidence rate of 2.04/1000 individuals/month (95% CI: 0.93, 3.88). Two cases were associated with systemic recurrence. The median follow-up was 29 months.

The median age of patients was 50.8 years, with four patients aged 50-65 years. Eight of nine patients were men. None of the nine patients was positive for HIV.

In this series, a significant number of patients had mediastinal masses (4/9). One patient had retroperitoneal disease and one had the lymphoma primarily located in the testicle. Eight patients in this small series had less than two extranodal sites affected and only three had bulky disease.

The average infiltration time was 7.9 months (range: 1-16 months), with a median of 7 months. In most cases (7/9) the infiltration was parenchymal.

Two (22.2%) patients had severe headaches, three (33.3%) had paraplegia or paraparesis, one (11.1%) in the left hand associated with the previously described headache and the other (11.1%) involving the VII cranial nerve bilaterally, one (11.1%) patient had ataxia with mental confusion and dysarthria.

Seven out of nine (77.7%) patients had stage III and IV disease. Despite the stage, six patients (33.3%) had IPI < 3. The bone marrow was involved in only one patient at diagnosis and LDH was increased in 8/9 (88.8%) patients. Four of the nine patients (44.4%) were refractory to the initial treatment, 3/9 (33.3%) achieved a complete response and 1/9 (11.1%) patient had partial response initially.

Among the nine patients, two (22.2%) underwent only imaging exams for the identification of CNS infiltration (due to contraindication for CSF exam) and seven (77.7%) had CSF testing associated to imaging. Of these, two (22.2%) were CSF-negative and five were positive. Among these, 2/9 (22.2%) had received IPC in the first three to four cycles of the infusion in the initial protocol.

In this series, five of the nine patients (55.5%) died and three were lost to follow-up. This probably was due to the fact they lived far away from our service and went back home when treatment had finished or their health had deteriorated with no curative treatment options. One patient, who had CNS infiltration and was submitted to high-dose chemotherapy and autologous hematopoietic stem cell transplantation, is still being seen in our service.

Survival after CNS infiltration was 1.9 months on average, with a median of 1.3 months.

Table 2 - Risk factors for central nervous system infiltration among patients with diffuse large B-cell lymphoma in the Santa Casa cohort: univariate analysis

Central nervous system outcome	Incidence	Rate of incidence	p-value
Age (years)			
< 60 years	2.9	reference	0.106
≥ 60 years	0.6	0.21 (0.03; 1.69)	
Gender			
Female	0.5	reference	0.034
Male	3.4	6.91 (1.86-55.28)	
Extranodal sites			
≤ 1	1.9	reference	0.594
≥ 2	3.4	1.75 (0.22-13.98)	
Bulky disease*			
No	1.7	reference	0.414
Yes	3.1	1.75 (0.44-7.07)	
Stage			
I/II	0.8	reference	0.037
III/IV	3.7	4.58 (1.95-22.03)	
B symptoms**			
No	1	reference	0.13
Yes	3	3.15 (0.66-15.18)	
International Prognostic Index			
0-2	2	reference	0.888
3-5	2.2	1.1 (0.28-4.42)	
Bone marrow biopsy			
Negative	2.1	reference	0.68
Positive	3.2	1.54 (0.19-12.34)	
Lactic dehydrogenase (g/dL)			
Normal	0.9	reference	0.321
Elevated	2.4	2.74 (0.34-21.93)	
Hemoglobin (g/dL)			
≥ 10.5	1.5	reference	0.027
< 10.5	6.4	4.2 (1.05-16.78)	
Albumin (g/dL)			
≥ 4	1.7	reference	0.919
< 4	1.5	0.92 (0.17-5.00)	
Beta-2-microglobulin (mg/L)			
Normal	1.4	reference	0.965
Increased	1.4	0.95 (0.09-10.45)	
Treatment			
Chemotherapy	3	3.85 (0.48-30.82)	0.17
Chemotherapy + radiotherapy	0.8	reference	
Response			
Complete	1	reference	
Partial	1.8	1.79 (0.19-17.16)	0.611
Refractory	8.7	8.74 (2.09-36.57)	< 0.001

* Bulky: mass size > 10 cm; ** B symptoms: night fever, night sweats and fever

Table 3 - Risk factors for central nervous system infiltration among patients with diffuse large B-cell lymphoma in the Santa Casa cohort: multivariate analysis

Central nervous system	Relative risk	95% confidence interval	p-value
Age at diagnosis			
< 60 years	reference		
≥ 60 years	0.188	0.022-1.606	1.127
Gender			
Female	reference		
Male	9.523	1.072-84.571	0.043
Hemoglobin (g/dL)			
≥ 10.5	reference		
< 10.5	4.299	0.957-19.319	0.057
Intrathecal chemotherapy			
No	reference		
Yes	12.531	1.951-80.466	0.008
Response			
Complete	reference		
Partial	2.243	0.211-23.805	0.503
Refractory	8.436	1.724-41.274	0.008

* Bulky: mass size > 10 cm; ** B symptoms: night fever, night sweats and fever

Risk factors for central nervous system infiltration in patients with diffuse large B-cell lymphoma

In the evaluation of the risk factors using the simple Mann-Whitney test to compare patients with and without CNS infiltration, it was possible to observe that there were significantly more men among the patients with infiltration (p-value = 0.043). The presence of a mediastinal mass was also significantly different between the two groups (p-value = 0.05): mediastinal masses were seen in 4/9 of the patients with infiltration. The other risk factors were not significantly different.

Of all the univariate analysis variables, those that exhibited a statistically higher incidence rates with significant p-values were being male (p-value = 0.034), advanced stage (p-value = 0.037), Hb < 10.5 mg/dL (p-value = 0.027), intrathecal chemotherapy (p-value = 0.047) and patient with refractory response to the initial treatment (p-value < 0.001). Regarding the final outcome, there was a higher incidence of deaths in patients with CNS infiltration (p-value = 0.002; Table 2). Mediastinal mass was not evaluated as the total number of patients with this presentation was too small to show any statistical differences.

In the multivariate analysis, the risk factors that were statistically significant were being male (p-value = 0.043), use of intrathecal chemotherapy (p-value = 0.008) and response pattern refractory to initial treatment (p-value = 0.008; Table 3).

Discussion

As already reported, infiltration of the CNS occurred in 6.7% of patients in the Santa Casa cohort with an incidence rate of 2.04 per 1000 individuals/month (95% CI: 0.93-3.88). As the median follow-up was 29 months and all cases occurred within 16 months, it can be considered that this index is quite representative of the patient population, with few missing cases.

Publications with larger cohorts show very different incidences of CNS infiltration, ranging from 1.1% to 10.4%[17-19,21-23,28]. In most studies, the median follow-up was three years or more, while our median follow-up was a little shorter but all our cases of infiltration occurred within 16 months after diagnosis.

A PubMed database search with the phrase "CNS

Involvement in diffuse large B-cell lymphoma" revealed 118 articles; of these, eight studies had designs similar to this cohort (Table 4). The number of patients in each series ranged from 259[5] to 1222[10]. Our study has fewer patients (133), but allowed the analysis of risk factors involved in infiltration.

The average age of patients in our study was lower than all other series reported, showing that, in our population, this disease began earlier. Most of our patients (54.1%) were in advanced stages (III and IV), similar to the series by Shimazu et al.[3] and Boehme et al.[10]. On the other hand, in the series of Arkenau et al.[5], Yamamoto et al.[9], Tai et al.[7] and Chihara et al.[11] the patients were mostly in early stages (I/II). Interestingly, two series (Feugier et al.[4] & Villa et al.[8]) had many patients in advanced stages. Regarding the IPI, our population was similar to the cohorts of Arkenau et al.[5], Yamamoto et al.[9], Chihara et al.[11] and Tai et al.[7]. In these studies, one-third of the patients had intermediate or high IPIs.

The most recently published article[11] built an association model of risk factors to better identify patients at high risk for infiltration. The study evaluated the risk factors by two different methods: one using the Kaplan-Meier (used in other studies mentioned above) and another through regression analysis of competitive risk, where the event of death was censured so that the rate of infiltration was not overestimated. By this method, Chihara et al.[11] obtained an infiltration rate of 6.7% with bulky disease, extranodal involvement, less than 1 x 10^9/L lymphocytes and extranodal relapse as risk factors shown in the multivariate analysis. The study of Chihara et al.[11] also used a model of association of risk factors (bulky disease, extranodal involvement and number of lymphocytes), and found a higher infiltration rate in the group with two or three risk factors; the use of rituximab had no protective effect.

Of all the studies mentioned previously, three[3,8,10] have shown that rituximab, when used in first-line treatment, reduces the risk of CNS infiltration, and four [4,7,9,11], that its use does not alter infiltration rates. In the study by Arkenou et al.[5], this analysis was not performed, because most patients received regimens without rituximab. In the Santa Casa cohort, only 17% of patients used this medication in combination with the CHOP regimen. With this small number of patients it was not possible to determine whether rituximab would be a protective factor or not for CNS infiltration.

The use of rituximab as a first-line treatment has been consolidated due to the higher rates of complete response and overall survival[29]. However, an association with a lower incidence rate of CNS infiltration has not been found yet. Better analyses of subgroups should be conducted to verify whether infiltration occurs early with the use of rituximab, which probably would indicate the presence of a hidden disease at diagnosis, a reason for the inefficiency of the medication.

Patients with DLBCL should be further investigated with more sensitive techniques to assess CSF, such as immunophenotyping and molecular biology exams, and probably more aggressive early treatment protocols could be offered to those at high risk of hidden disease thereby reducing infiltration rates. This issue was evaluated in the study by a Nordic group, which analyzed the risk factors for infiltration in high and very high grade lymphomas. The researchers described that in the presence of three or more risk factors (increased LDH, age > 60 years, more than one extranodal site, retroperitoneal involvement and hypoalbuminemia), the chance of infiltration exceeds 25%[18]. Studying specifically the high-risk subgroup, two studies have showed fairly low infiltration rates in patients who used more aggressive treatment protocols[30,31].

Only one article mentioned above discusses whether risk factors should be considered individually (i.e. in the presence of one risk factor, the intervention or further observation would be indicated) or if two or three factors indicate a significantly higher chance of infiltration. Moreover, no study states the percentage of patients who had no risk factors analyzed and the presence of CNS infiltration within this group. Objectively, further studies are still needed to assess and more precisely identify which patients, among all individuals with DLBCL, are at higher risk for CNS infiltration. This must be done through the study of grouped risk factors and a more sensitive assessment of hidden disease in the CNS. After this identification, several research groups should make further analysis with more aggressive treatment protocols, as this is a rare event, before determining the treatment protocol.

This study has some limitations, mainly related to the small number of cases, to the retrospective design and to the heterogeneity of the sample and treatments administered. These features may have limited the interpretation of significance on the use of IPC. The use of IPC had greater impact on CNS infiltration risk, possibly because,

Table 4 - Studies that investigated central nervous system infiltration among patients with diffuse large B-cell lymphoma

Author	n	Age (years)	Stage III-IV (%)	IPI intermediate/ high (%)	CNS infiltration (%)	R
Feugier et al.[4]	399	47% > 70	79	60	5	no
Arkenou et al.[5]	259	62 (mean)	42	36	1.1	NR
Shimazu et al.[3]	399	71 (mean)	56	49	10.4	yes
Boehme et al.[10]	1.222	36% > 70	50.5	41.7	4.8	yes
Villa et al.[8]	435	65 (mean)	70	61	7.1	yes
Yamamoto et al.[9]	375	66.4% > 60	39.2	35.4	3.5	no
Tai et al.[7]	499	60% > 60	44	26	CHOP: 5.1 RCHOP: 6.0	no
Chihara et al.[11]	386	54% > 60	41	31	7.9	no
Current study (2011)	133	52.4 (mean)	54.1	36.7	6.7	NR

CNS: Central nervous system; IPI = International Prognostic Index; R = rituximab as protective factor; NR = not reported

as there was no formal protocol for the use of IPC, only patients with very high risk of infiltration (with many risk factors) were submitted to this prophylaxis. This is the first Brazilian study that evaluates the incidence of infiltration and its possible risk factors.

Conclusion

The incidence of CNS infiltration by DLBCL observed in this cohort was 6.7%, which is similar to other previously published cohorts. In multivariate analysis, this study found being male and refractory response to the initial treatment are risk factors for CNS infiltration. The cohort of patients diagnosed with DLBCL analyzed here is consistent with the data of similar studies and, thus, appropriate for the study of cases.

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