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Head and Neck Presentations of B-NHL and B-AL in Children/Adolescents: Experience of the LMB89 Study

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Purpose. Describe the epidemiology, clinical profiles and outcomes associated with head and neck (H&N) involvement in children/adolescents with B-cell non-Hodgkin lymphoma (B-NHL). ***Methods.*** Analysis of children/adolescents with H&N B-NHL prospectively enrolled in the SFOP LMB-89 trial (July 1989–June 1996). ***Results.*** One hundred and twelve of 561 patients (20%) had H&N involvement. The mean age of the patients was 8.4 years. Murphy staging differed between the H&N patients and the others ($P < 0.0001$): 9% versus 5% of the patients presented with stage I disease, 36% versus 11% presented with stage II disease, 12% versus 59% presented with stage III disease, 17% versus 10% with stage IV disease and 27% versus 16% with B-AL. Twenty-nine H&N patients (26%) had CNS involvement at diagnosis versus 8.5% in the group without H&N involvement ($P < 0.0001$). Patients were treated according to the LMB89 protocol: 3 H&N patients were allocated to group A, 70 to group B and 39 to group C. Ninety-seven percent of H&N patients achieved CR and event-free and overall survival at 4 years was 95.5% (5 deaths in patients with CNS disease). On multivariate analysis, EFS was significantly better in H&N patients than in non-H&N patients ($P = 0.021$), but not OS ($P = 0.11$). ***Conclusion.*** The H&N site is the second most common location for B-NHL at diagnosis and is more frequently associated with disseminated disease and CNS involvement than other sites. However, outcomes are no worse for these patients than for the rest of the population. Pediatr Blood Cancer 2014;61:473–478.

Key words: B-cell non Hodgkin's lymphoma; chemotherapy; children; head and neck cancer

INTRODUCTION

High-grade malignant non-Hodgkin lymphoma (NHL) accounts for approximately 8% of all childhood cancers diagnosed each year in France [1]. The most frequent forms are B-cell NHL (B-NHL), such as Burkitt, Burkitt-like or B-large cell lymphomas. Since 1981, all children with B-NHL in France have received intensive chemotherapy according to the protocols of the French Society of Paediatric Oncology (SFOP) [2–6]. The results of the national multicenter LMB89 trial, which is at the origin of the current treatment protocol, showed that 92.5% of the children or adolescents with this type of lymphoma can be cured [5]. The head and neck (H&N) is the second most common disease site after the abdomen [5,7]. This form, which is particularly challenging because of the risks of airway obstruction and the proximity of the meninges, was evaluated in a previous French retrospective single centre study which reported a significantly higher rate of CNS involvement in H&N NHL patients than in non-H&N patients (25% vs. 5%) [8]. It is well known that CNS involvement is a poor prognostic sign in NHL patients. Thus, it could be expected that patients with H&N involvement would fare less well than the others. In this paper, we present the epidemiological, clinical and prognostic profiles of children and adolescents with H&N involvement and B-NHL or mature B-cell acute leukaemia (B-AL, previously referred to as L3-ALL in the French–American–British classification) included in the prospective LMB89 multicentre study so their symptoms could be described and compared to those of patients without H&N involvement.

PATIENTS AND METHODS

Patients

From July 1989 to June 1996, 561 consecutive untreated patients (436 boys and 125 girls) with B-NHL or B-AL and under the age of 18 were included in the SFOP LMB89 study by 38 SFOP and affiliated paediatric oncology units [5]. Central nervous system involvement was defined as the presence of blasts in the cerebrospinal fluid (CSF), cranial nerve palsy (CNP) not related to a facial tumour, clinical signs of spinal cord compression or intracranial extension (ICE). B-cell acute leukaemia was defined as the presence of >25% of blasts in the bone marrow. Primary H&N involvement was defined as main H&N lesions at the time of initial diagnosis and secondary H&N involvement as H&N involvement found during the staging workup in patients with primary involvement elsewhere. Isolated cervical adenopathies or H&N skin lesions were not defined as H&N involvement in line with the criteria of the LMB89 study.

Treatment

Details of the LMB 89 regimen that have already been published are not given here, but the general treatment scheme is shown in Figure 1 [5]. Patients were stratified into three therapeutic risk

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groups according to tumour status: Group A (patients having undergone complete resection of stage I and abdominal stage II disease), Group B (patients with unresected stage I, non-abdominal stage II and any stage III or IV disease and B-AL CNS - (with <70% of blasts in bone marrow)) and Group C (CNS involvement or B-AL with at least 70% of blasts in bone marrow) (Fig. 1).

Response to treatment was evaluated twice. The first evaluation was at D7 after the prephase COP regimen. Patients in group B whose disease did not respond to the prephase COP regimen (response inferior to 20%) were switched to group C. Complete remission had to be assessed after the first CYM in group B and the second CYVE in group C. If the patients presented with a residual mass, it had to be removed to evaluate the presence of viable cells which would lead to treatment intensification with high-dose chemotherapy (HDCT) and autologous bone marrow transplantation. The preparative regimen was the BEAM regimen (BCNU, VP16, Ara-C and melphalan).

METHODS

Epidemiological, clinical and therapeutic data and outcomes were extracted from the LMB89 study database. Clinical staging at diagnosis was determined according to the St. Jude system [9]. Histological diagnosis was reviewed by a national panel of experts using the updated Kiel classification [10] and then the REAL classification [11] and the tumours were subclassified as Burkitt lymphoma or large B-cell lymphoma. Some cases could not be subclassified, generally because of technical problems, and were assessed as 'unclassified high-grade B-cell lymphomas'. Tumour burden was estimated by measurement of serum lactate dehydrogenase (LDH) and its ratio compared to the upper limit of normal range of the laboratory.

Statistical Methods

Data from the LMB89 database were used for comparisons between patients with H&N and without H&N involvement. Patient and tumour characteristics were compared for patients with H&N involvement and for patients without H&N involvement using the Chi-square or Fisher's exact tests for qualitative variables and the *t*-test for quantitative variables. Central nervous system and CSF involvement was compared between patients with and without H&N involvement using logistic regression analysis with adjustments being made for age, gender, pathological diagnosis and LDH levels.

Overall survival (OS) was calculated from the first day of chemotherapy to the date of death or the date of last follow-up for alive patients. Event-free survival (EFS) was calculated from the first day of chemotherapy to the date of the first event (progression after partial response, relapse, second malignancy or death from any cause) or to the date of last follow-up for event-free patients. OS and EFS rates were estimated using the Kaplan–Meier method [12]. EFS and OS comparisons between patients with and without H&N involvement were performed using the log rank test [13] for univariate analyses and the Cox model for multivariate analyses taking into account the prognostic factors identified in the LMB89 study, that is, the therapeutic risk group (A, B, C); LDH levels ($\leq$twofold the upper limit of normal vs. >twofold the upper limit of normal); CNS involvement (no vs. yes); age (<15 years vs. $\geq$15 years); no response to COP (no response vs. response or no COP for group A) [5]. All statistical tests were two sided. Analyses were performed using SAS Software, version 9.1.

RESULTS

Patients

Of 561 patients with B-NHL or B-AL, 112 presented H&N involvement as defined previously. Ninety-four had primary H&N involvement and 18 had secondary involvement (6 primary abdominal lymphomas, 1 primary renal lymphoma and 11 primary leukaemias).

H&N Localization and Diagnosis Modalities

Ninety out of 112 patients (80%) presented isolated H&N lesions: 37 patients had lesions in the tonsils, 23 in the nasopharyngeal area, 18 in the maxillae or mandibles, 10 in other sites (orbit: 3, lacrymal sac: 1, parotid gland: 1, ethmoid bone: 2, retropharynx: 1, thyroid: 2) and 2 in unknown localisations. Twenty-two patients (20%) presented multiple H&N lesions,

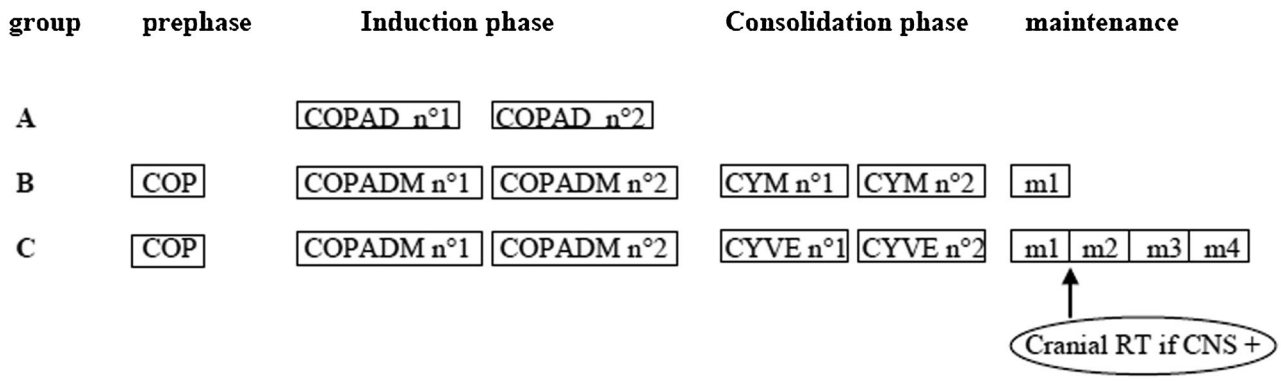

Fig. 1. LMB89 treatment regimen. COP: cyclophosphamide, Oncovin (vincristine), prednisone ; COPAD: cyclosphamide, Oncovin, prednisone, Adriamycine (doxorubicin) ; COPADM: cyclosphamide, Oncovin, prednisone, Adriamycine, methotrexate ; CYM: cytarabine, methotrexate ; CYVE: cytarabine, etoposide; m1: maintenance course 1 (cyclosphamide, vincristine, prednisone, doxorubicin, methotrexate); m2: maintenance course 2 (cytarabine, etoposide); m3: maintenance course 3 (cyclophosphamide, vincristine, prednisone, doxorubicin); m4: maintenance course 4 (similar to m2); RT: radiotherapy; CNS: central nervous system.

TABLE I. H&N Locations and Involved Sites

Disease site	
Tonsil	37 (33%)
Cavum	23 (20.5%)
Maxilla	16 (14%)
Orbit	3 (3%)
Lacrimal sac	1 (1%)
Parotid gland	1 (1%)
Ethmoid	2 (2%)
Retropharynx	1 (1%)
Thyroid	2 (2%)
Periodontium	2 (2%)
Unknown	2 (2%)
Multiple	22 (19.6%)
Involved associated sites	
Cervical nodes	62 (55%)
Kidney	22 (19.6%)
Liver	14 (13%)
Spleen	9 (8%)
Ovary	2 (2%)
Testis	4 (3.5%)

including 1 patient who presented extended involvement of the cavum, maxilla and mandible (Table I). The mean symptom to diagnosis time interval (all lesions combined) was 27.8 days (range: 3–120). Only one patient required mechanic ventilation. Nine children received corticosteroids before the diagnosis of NHL; the median duration of corticosteroid administration was 4 days (range: 3–8).

Of the 94 children with primary H&N involvement, 85 underwent initial surgical procedures, that is, 27 patients (29%) underwent tumour resections (13 partial resections and 14 complete or major resections [>90% of the tumour volume]) and 58 patients underwent surgical biopsies. In the remaining nine patients, diagnosis was made by needle aspiration of the primary tumour (one case) or lymph node (three cases), or by bone marrow smear examination (five cases). The involved sites other than the H&N are reported in Table II. Of note, 22 patients had renal lesions (19.6%) versus 46 (10.2%) in the remaining population ($P = 0.0064$).

Characteristics of the Patients and Comparison With Patients Without H&N Involvement

Most children (98 patients, 87.5%) were Caucasian. The mean age of the children was 8.4 years (range: 2–17.7) and the male to female ratio was 4.6. Ninety patients (80%) were diagnosed with Burkitt lymphoma, 13 patients (11.6%) were diagnosed with diffuse large B-cell lymphoma and 9 patients (8%) with unclassified high-grade B-cell lymphoma. This is no different from the rest of the LMB 89 population.

TABLE II. H&N Patients Characteristics Versus Non-H&N Patients

Characteristics	H&N patients	Non-H&N patients	*P*
Sex ratio			
Males	92 (82%)	344 (77%)	0.21
Females	20 (18%)	105 (23%)	
Age			
Mean [range]	8.4 [2–17.7]	8.8 [0.1–18]	0.40
Stage			
I	10 (9%)	21 (5%)	<0.0001
II	40 (36%)	48 (11%)	
III	13 (12%)	265 (59%)	
IV	19 (17%)	43 (10%)	
IV CNS	11	12	
IV BM	5	26	
IV BM & CNS	3	5	
B-AL	30 (27%)	72 (16%)	
B-AL CNS	15	21	
Histological type			
Burkitt	90 (81%)	333 (79%)	0.59
DLBCL	13 (12%)	50 (11%)	
Unclassified high grade B-NHL[a]	9 (8%)	46 (10%)	
LDH			
>2 N	39 (36%)	219 (53%)	0.0016
≤2 N	69 (64%)	193 (47%)	
Unknown	4	37	
CNS	29 (26%)	38 (8.5%)	<0.0001
CSF	15 (13.4%)	22 (4.9%)	0.0012
CNP	22 (19.5%)	16 (3.6%)	<0.0001
Isolated CNP	6 (5.4%)	9 (2%)	0.092
ICE	9 (8%)	4 (0.9%)	<0.001

IV NM, Stage IV with CNS involvement only; IV BM, Stage IV with bone marrow involvement only (<25% blasts in the bone marrow); IV BM + CNS, Stage IV with bone marrow and CNS involvement; B-AL, Mature B-cell Acute leukaemia (>25% blasts in the bone marrow); B-AL + CNS, B-AL with CNS involvement; DLBCL, Diffuse large B-cell lymphoma; CSF, presence of blasts in the cerebro-spinal fluid; CNP, cranial nerve palsy; ICE, intra-cranial extension. [a]Eligible for the study because diagnosed as high-grade B-NHL.

According to the St Jude classification system, 10 patients (9%) had stage I NHL (only 3 completely resected), 40 (35.5%) had stage II disease, 13 (11.5%) stage III disease, 19 (17%) stage IV disease and 30 (27%) B-AL. Of the patients with stage IV disease, 11 (58%) presented with CNS involvement, 5 with bone marrow involvement (<25% blasts) and 3 with both. Of the 30 children with B-AL, 15 (50%) had CNS involvement. Thus, 38 patients presented with bone marrow involvement and 29 patients (26%) with CNS involvement. Central nervous system involvement included the presence of blasts in CSF in 15 patients (13.4%), CNP (6 isolated) in 22 patients (19.6%) and ICE in 9 patients (8%). Among the cases of cranial nerve palsies, six patients presented with isolated CNP and two patients with only hypoaesthesia or anaesthesia of the chin (V_3).

Baseline LDH Levels Were More Than TwoFold the Upper Limit of the Normal Laboratory Range in 36% of Cases

Several of these characteristics differ significantly from the rest of the LMB 89 population, that is, stage distribution, with more stages I and II and stages IV and B-AL, more CNS involvement including more frequent occurrences of blasts in the CSF, CNP and ICE. Conversely, the percentage of patients with high LDH levels was lower (Table II). The difference in CNS and CSF involvement between patients with H&N involvement (respectively 26% and 13.4%) and those without H&N involvement (respectively 8.5% and 4.9%) remained significant on multivariate analysis of the data.

Outcomes

Three patients were treated in group A, 70 in group B and 39 in group C. Response to the prephase COP regimen was not evaluated or was not evaluable in 12 patients. Of the 100 assessed patients, only 1 (initially treated in group B) presented with disease that showed no response. A total of 109 patients (97.3%) achieved a CR: 108 with the planned protocol at the planned time and 1 (initially treated in group B) after HDCT following observation of partial remission with documented viable cells in the residual mass at the time of CR assessment. At the time of CR assessment, 23 patients had residual tumour masses but viable cells were detected in only one of the 21 analysed masses. Three patients never achieved CR and died, they had CNS involvement at diagnosis (2 had blasts in the CSF and 1 had CNP) and showed disease progression despite therapy.

Altogether, five patients died, all of them presented CNS involvement at diagnosis. In four cases, the children died because of the disease: three patients did not achieve CR, and one patient (with blasts in the CSF and CNP at diagnosis) achieved CR but presented early relapse of the disease in the bone marrow and testis (within 4 months of diagnosis) and died within 6 months of diagnosis. The fifth patient (with CNP at diagnosis) died suddenly of congenital atrioventricular block following complete remission. No deaths or events were identified between diagnosis and the initiation of treatment. The EFS and OS rates at 4 years were identical: 95.5% [95% CI, 90–98%].

Comparison of Outcomes Between Patients With H&N Involvement and Those Without H&N Involvement

The percentage of good responders to COP tended to be higher in patients with H&N involvement than in those without H&N involvement (99% vs. 94.5%) ($P = 0.059$) but the 97% percentage of patients who achieved a CR was similar. Univariate analysis showed that EFS was not significantly different between children with H&N involvement and the others in LMB89 protocol, with a hazard ratio (HR) of 0.42 [95% CI = 0.17–1.05] ($P = 0.064$) and 4-year rates of respectively 95.5% [95% CI, 90–98%] and 90.1% [95% CI, 87–93%]. OS was not significantly different between the two populations with a HR of 0.55 [95% CI = 0.22–1.41] ($P = 0.21$) and 4-year rates of respectively 95.5% [95% CI, 90–98%] and 92% [95% CI, 90–95%]. In the multivariate analysis of the therapeutic risk group, of CNS involvement, LDH levels, age and no response to COP, the HR for EFS became significant in favour of patients with H&N involvement, that is, equal to 0.32 [95% CI = 0.12–0.85] ($P = 0.021$). However, in terms of prognostic factors for OS, the HR was still not significant, that is equal to 0.45 [95% CI = 0.17–1.21] ($P = 0.11$) (Fig. 2).

Among patients with CNS involvement treated according to the LMB89 protocol, EFS was not significantly different between

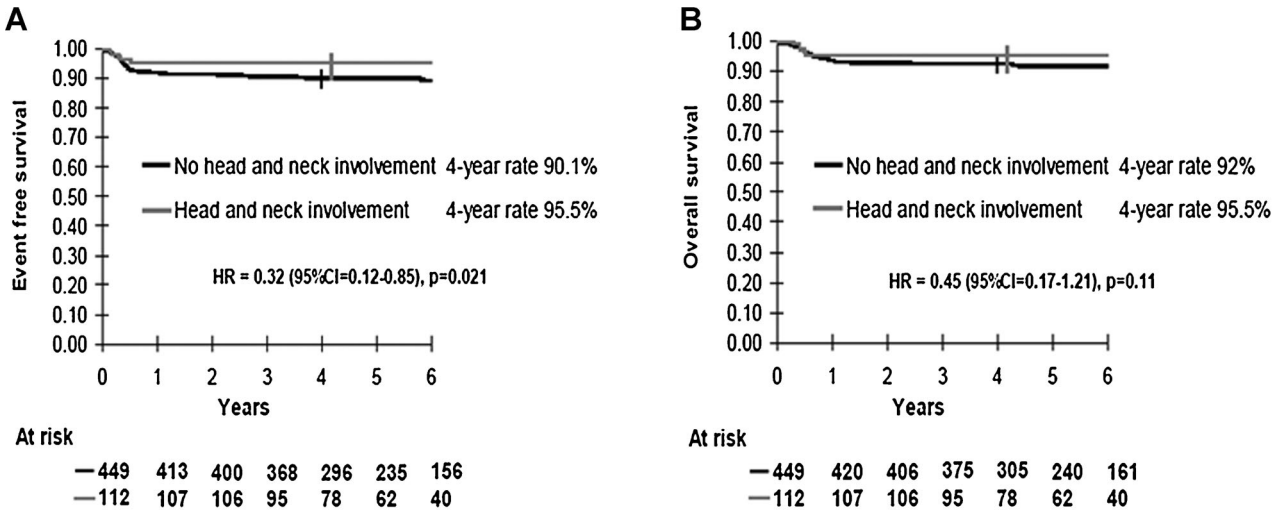

Fig. 2. Event-free (**A**) and overall survival (**B**) of patients with or without head and neck involvement. Hazard ratio (HR) of H&N patients versus non-H&N patients, adjusted for known prognostic factors (risk group, CNS involvement, LDH level, age, response to COP).

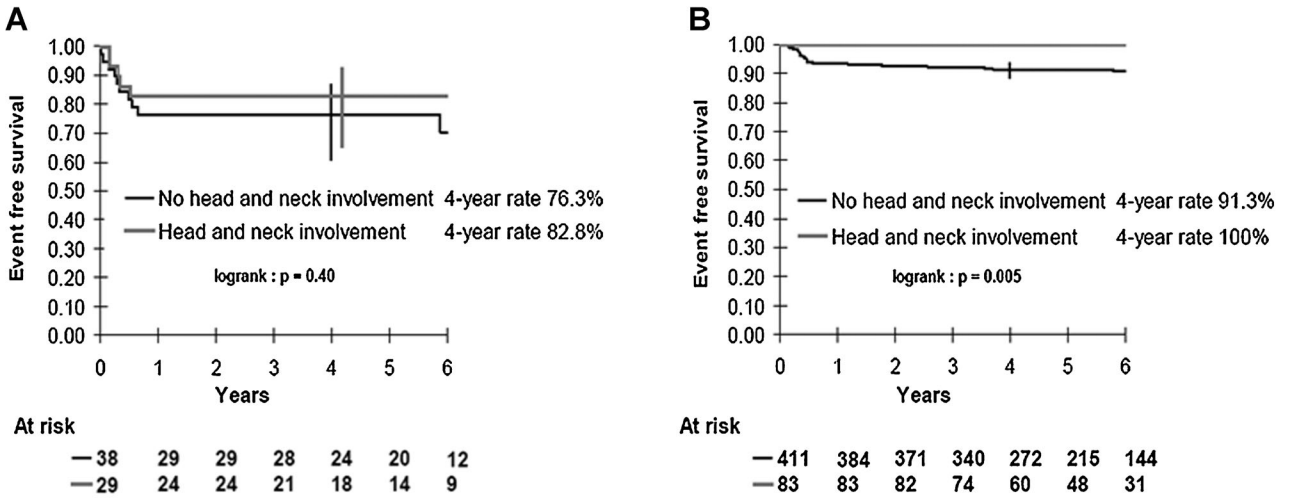

Fig. 3. Event-free survival of patients with or without head and neck involvement according to the presence (**A**) or the absence (**B**) of CNS involvement.

patients with H&N locations and non-H&N locations ($P = 0.40$). The HR was 0.63 [95% CI = 0.22–1.85] and the 4-year EFS rates were respectively 82.8% [95% CI, 66–92%] and 76.3% [95% CI, 61–87%]. The results were the same for OS (HR = 0.72 [95% CI = 0.24–2.13], $P = 0.55$). In patients without CNS involvement, EFS and OS were significantly better in patients with H&N involvement than in other patients: 4-year EFS rates of 100% and 91.3% respectively ($P = 0.005$) and 4-year OS rates of 100% and 93.9% respectively ($P = 0.018$) (Fig. 3).

DISCUSSION

Primary H&N involvement was observed in 16.7% of all patients enrolled in the LMB89 study, which is in agreement with the 18% rate identified in the earlier single centre study by Bergeron et al. [8]. Other studies produced potentially different results: two single centre trials published by American [14] and Turkish [15] authors showed that 9% of patients presented H&N NHL; Murphy et al. [16] and Link et al. [17] reported much higher rates (22% and 33% respectively), but both studies also included patients with only cervical node involvement. In a series of 445 patients with NHL, the Paediatric Oncology Group identified 221 patients with H&N involvement, but without providing a definition of what was considered as H&N involvement [18]. Nevertheless, taken together, our results and data from the literature confirm that H&N B-NHL is the second most common form of B-NHL in children (after abdominal involvement) [7]. As with other forms of the disease, there is a higher incidence in males, with a male to female ratio of 5 to 1. The distribution of histological types was similar to other B-NHL, with Burkitt lymphomas being the predominant type [7,19].

Significant improvements have been made in the diagnosis of H&N NHL over the past years. The median time to diagnosis was reduced from 56 days in a previous report by Bergeron et al. [8] to 27.8 days. Compared to 8/63 patients who underwent tracheotomy in the previous study, only one patient required mechanic ventilation. Common symptoms such as persistent nasal obstruction in children must lead to screening for a nasopharyngeal tumour [20,21]. Ten percent of our patients had received previous corticosteroid treatment.

In the present series, among the isolated H&N involvement sites, the most frequently affected site was the tonsils (37/94), followed by nasopharynx (23/94), contrary to the results of the previous series [8] where the nasopharynx was identified as the first site (51%).

Clinical staging of our 112 patients with H&N involvement showed significant differences compared to the rest of the LMB89 patients, with the H&N patients presenting more stage I and stage II tumours. This high number of patients with stage I and II disease (small volume tumours) likely accounts for the lower LDH levels in patients with H&N involvement. In contrast, we found more stage IV lymphomas and B-AL.

We also showed that either primary or secondary H&N involvement was associated with CNS involvement at diagnosis in 26% of the patients versus 8.5% of non-H&N patients. This is consistent with results of the previous single centre series which reported rates of 25% versus 5% respectively [8].

The clinical significance of isolated cranial nerve involvement may be debatable. Anaesthesia of the chin with or without pain (numb chin syndrome) is a common symptom of blood cancers, particularly of Burkitt leukaemia [22–25]. It is caused by major infiltration and destruction of the axon and myelin of the mandibular nerve by leukaemic cells [24] but without CNS involvement. The German BFM-86 study did not include patients with cranial nerve lesions in the group with CNS involvement [26] contrary to the subsequent BFM-90 study [27]. Isolated cranial nerve lesions were not identified as CNS involvement in the CCG-551 trial [28], but this was not the case in the CCG-552 trial in which CNS disease was defined by either the presence of lymphoblasts in the CSF or by the presence of cranial neuropathies [29].

Our hypothesis of a possible overestimation of CNS disease because of cranial nerve involvement cannot completely account for the discrepancy between the incidence of CNS lesions in H&N patients and in the other patients in the LMB89 study. Patients with H&N involvement also had more frequent infiltration of the CSF by leukaemic cells than other patients (13.4% vs. 5%), whereas previous studies did not demonstrate a correlation between CNS

and H&N involvement [18,30]. In patients with B-NHL, CNS involvement was associated with a poorer prognosis [3,5,6,18,27]. Indeed all the events observed occurred in patients with CNS involvement.

We have showed that the prognosis of patients with H&N involvement was not worse than the prognosis of the other patients. Even after adjustment for known prognostic factors (risk group, CNS involvement, LDH level, age, response to COP), the EFS of patients with H&N involvement was significantly better than the EFS of patients without H&N involvement: HR = 0.32, $P = 0.021$. There was no significant difference for OS between the two groups after adjustment (HR = 0.45, $P = 0.11$). In the LMB89 study, only patients with CNS involvement received cranial RT. This study demonstrates that, contrary to the findings of an Indian study published in 2008 [31], patients with H&N NHL without CNS involvement may have a very satisfactory outcome without radiotherapy. It must also be remembered that in the subsequent LMB studies, especially the FAB/LMB96 international study, radiotherapy was no longer used [6]. In a previous cohort published by Traggis et al. [32], major survival differences were observed between patients with H&N disease and those with other forms of NHL whose life expectancy was low at the time (51.7% and 9% respectively). In 1990, Wollner et al. confirmed the prognostic advantage of H&N involvement over other NHL presentations, with EFS rates as high as 85% with a median follow up of 8.5 years in patients on non-optimal BNHL LSA2-L2 treatment; of note, no CNS involvement was reported in their cohort [14]. The OS differences between patients with H&N and those without H&N involvement described in previous studies are no longer observed since the use of multiagent intensive therapy. In our study using intensive therapy, we found that H&N could have a possible prognostic impact.

In conclusion, this analysis of 112 cases of NHL and B-AL with H&N involvement among patients from the LMB89 cohort has provided a more precise description of this clinical entity: H&N involvement is associated with lower stage disease than other locations but also with more frequent CNS involvement. Central nervous system involvement remains a poor prognostic factor, nevertheless the outcome of children/adolescents with H&N NHL was no worse than the outcome of those without H&N involvement.

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REFERENCES

1. Clavel J, Goubin A, Auclerc MF, et al. Incidence of childhood leukaemia and non-Hodgkin's lymphoma in France: National registry of childhood leukaemia and lymphoma, 1990–1999. Eur J Cancer Prev 2004;13:97–103.
2. Patte C, Philip T, Rodary C, et al. High survival rate in advanced-stage B-cell lymphomas and leukemias without CNS involvement with a short intensive polychemotherapy: Results from the French pediatric oncology society of a randomized trial of 216 children. J Clin Oncol 1991;9:123–132.
3. Patte C, Philip T, Rodary C, et al. Improved survival rate in children with stage III and IV B cell non-Hodgkin's lymphoma and leukemia using multi-agent chemotherapy: Results of a study of 114 children from the French Pediatric Oncology Society. J Clin Oncol 1986;4:1219–1226.
4. Patte C, Leverger G, Perel Y, et al. Updated results of the LMB86 protocol of the French Society of Pediatric Oncology (SFOP) for B-cell non-Hodgkin's lymphoma with CNS involvement and B-ALL [abstract]. Med Pediatr Oncol 1990;18:397.
5. Patte C, Auperin A, Michon J, et al. The Societe Francaise d'Oncologie Pediatrique LMB89 protocol: Highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphomas and L3 leukemia. Blood 2001;97:3370–3379.
6. Cairo MS, Gerrard M, Sposto R, et al. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. Blood 2007;109:2736–2743.
7. Sandlund JT, Downing JR, Crist WM. Non-Hodgkin's lymphoma in childhood. N Engl J Med 1996;334:1238–1248.
8. Bergeron C, Patte C, Caillaud JM, et al. Clinical, anatomo-pathologic aspects and therapeutic results in 63 malignant ORL non-Hodgkin's lymphomas in children. Arch Fr Pediatr 1989;46:583–587.
9. Murphy SB, Classification staging and end results of treatment of childhood non-Hodgkin's lymphomas: Dissimilarities from lymphomas in adults. Semin Oncol 1980;7:332–339.
10. Stansfeld A, Diebold J, Kapanci Y, et al. Updated Kiel classifications for lymphomas. Lancet 1988;331:292–293 [Erratum in: Lancet, 331:372].
11. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: Summary and description of a working formulation for clinical usage. The Non-Hodgkin's Lymphoma Pathologic Classification Project. Cancer 1982;49:2112–2135.
12. Kaplan E, Meier P. Non parametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481.
13. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples. Br J Cancer 1977;35:1–39.
14. Wollner N, Mandell L, Filippa D, et al. Primary nasal-paranasal oropharyngeal lymphoma in the pediatric age group. Cancer 1990;65:1438–1444.
15. Yaris N, Kutluk T, Yalcin B, et al. Nasal-paranasal-oronasopharyngeal lymphomas in childhood: The role of staging system on prognosis. Pediatr Hematol Oncol 2000;17:345–353.
16. Murphy SB, Fairclough DL, Hutchison RE, et al. Non-Hodgkin's lymphomas of childhood: An analysis of the histology, staging, and response to treatment of 338 cases at a single institution. J Clin Oncol 1989;7:186–193.
17. Link MP, Shuster JJ, Donaldson SS, et al. Treatment of children and young adults with early-stage non-Hodgkin's lymphoma. N Engl J Med 1997;337:1259–1266.
18. Sandlund JT, Murphy SB, Santana VM, et al. CNS involvement in children with newly diagnosed non-Hodgkin's lymphoma. J Clin Oncol 2000;18:3018–3024.
19. Brousse N, Vasiliu V, Michon J, et al. Pediatric non-Hodgkin lymphomas. Ann Pathol 2004;24:574–586.
20. Wu K, Majumdar S, Bull PD. Blocked nose and snoring in a 6-year-old boy. Int J Pediatr Otorhinolaryngol 2004;68:597–600.
21. Reichman OS, Goldin AD, Bayles SW, et al. Non-Hodgkin's lymphoma presenting as facial swelling and nasal obstruction in a pediatric patient. Otolaryngol Head Neck Surg 1999;121:127–129.
22. Seixas DV, Lobo AL, Farinha NJ, et al. Burkitt leukemia with numb chin syndrome and cavernous sinus involvement. Eur J Paediatr Neurol 2006;10:145–147.
23. Landesberg R, Yee H, Datikashvili M, et al. Unilateral mandibular lip anesthesia as the sole presenting symptom of Burkitt's lymphoma: Case report and review of literature. J Oral Maxillofac Surg 2001;59:322–326.
24. Kuroda Y, Fujiyama F, Ohyama T, et al. Numb chin syndrome secondary to Burkitt's cell acute leukemia. Neurology 1991;41:453–454.
25. Iwatsuji K, Fukuyama H, Shio H, et al. A case of Burkitt's lymphoma with numb chin syndrome as the initial manifestation. Rinsho Shinkeigaku 1989;29:764–768.
26. Reiter A, Schrappe M, Parwaresch R, et al. Non-Hodgkin's lymphomas of childhood and adolescence: Results of a treatment stratified for biologic subtypes and stage—A report of the Berlin-Frankfurt-Munster Group. J Clin Oncol 1995;13:359–372.
27. Reiter A, Schrappe M, Tiemann M, et al. Improved treatment results in childhood B-cell neoplasms with tailored intensification of therapy: A report of the Berlin-Frankfurt-Munster Group Trial NHL-BFM 90. Blood 1999;94:3294–3306.
28. Anderson JR, Wilson JF, Jenkin DT, et al. Childhood non-Hodgkin's lymphoma. The results of a randomized therapeutic trial comparing a 4-drug regimen (COMP) with a 10-drug regimen (LSA2-L2). N Engl J Med 1983;308:559–565.
29. Finlay JL, Anderson JR, Cecalupo AJ, et al. Disseminated nonlymphoblastic lymphoma of childhood: A Childrens Cancer Group study, CCG-552. Med Pediatr Oncol 1994;23:453–463.
30. Gururangan S, Sposto R, Cairo MS, et al. Outcome of CNS disease at diagnosis in disseminated small noncleaved-cell lymphoma and B-cell leukemia: A Children's Cancer Group study. J Clin Oncol 2000;18:2017–2025.
31. Laskar S, Bahl G, Muckaden MA, et al. Non-Hodgkin's lymphoma of Waldeyer's ring in children: Outcome using chemotherapy and involved field radiotherapy. Clin Oncol (R Coll Radiol) 2008;20:613–618.
32. Traggis D, Jaffe N, Vawter G, et al. Non-Hodgkin lymphoma of the head and neck in childhood. J Pediatr 1975;87:933–936.