**ORIGINALS**

Prospective study on the practice of central nervous system prophylaxis and treatment in non-Hodgkin’s lymphoma in Spain

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**BACKGROUND AND OBJECTIVE**: Central nervous system (CNS) involvement in patients diagnosed with non-Hodgkin’s lymphoma (NHL) or other lymphoproliferative disorders is an frequent complication with a poor prognosis. The prophylaxis and treatment of CNS involvement in these patients are not homogeneous. The aim of this prospective longitudinal study was to report the current practice of CNS prophylaxis and treatment in patients with lymphoproliferative disorders in Spain.

**METHODS**: Prospective study conducted from June 2005 to June 2006. Adult patients (a 18 yr) diagnosed with NHL or other lymphoproliferative disorders who received CNS prophylaxis or treatment were consecutively included through online registration.

**RESULTS**: Two hundred and twenty-eight patients from 33 hospitals were included. The mean (SD) age was 52 (16) yr and 144 (63%) were males. CNS therapy was given to 41 cases and consisted of triple intrathecal (ITT) therapy (ITT, methotrexate, cytarabine and hydrocortisone) in 22, liposomal depot cytarabine in 18 and methylprednisolone in one. In addition, 4 patients received cranial radiotherapy. CNS prophylaxis (n = 187) consisted of ITT (166 cases), ITT methotrexate (17), ITT liposomal depot cytarabine (3) and ITT cytarabine (1), whereas cranial or craniospinal radiotherapy was administered to 2 patients. The main reasons for CNS prophylaxis cited by the investigators included extranodal involvement (89 patients), raised serum lactate dehydrogenase level (87), IP scores > 2 (62), bulky mass (43), extranodal involvement in more than one organ (33) and poor or very poor Prognostic Index (PI) score (46), in 63% were males. CNS prophylaxis was given to 41 cases and consisted of triple intrathecal (ITT, methotrexate, cytarabine and hydrocortisone) in 22, liposomal depot cytarabine in 18 and methylprednisolone in one. In addition, 4 patients received cranial radiotherapy. CNS prophylaxis (n = 187) consisted of ITT (166 cases), ITT methotrexate (17), ITT liposomal depot cytarabine (3) and ITT cytarabine (1), whereas cranial or craniospinal radiotherapy was administered to 2 patients. The introduction of the new formulations of drugs, especially liposomal depot cytarabine for CNS involvement, and the scarce use of radiotherapy are also of note. Similar to other studies, the absence of homogeneous criteria for CNS prophylaxis is of note.

**CONCLUSIONS**: Consensus on CNS prophylaxis and treatment in patients diagnosed with non-Hodgkin’s lymphoma (NHL) occurs in about 5% of all patients, either at the time of diagnosis of NHL or during the course of progressive disease. In addition to the well-recognized poor prognosis of the patients with NHL and CNS involvement, this complication has been associated with a reduction in the quality of life due to both CNS involvement itself and to the side effects of CNS-directed therapies such as cranial irradiation, intrathecal (IT) drugs and systemic therapy with drugs able to cross the blood-brain barrier.

**Risk factors for lymphomatous meningitis have been identified from the analysis of large case series**.11 Histology is cited as one of the main risk factors, and thus, patients with certain high-grade histologic subtypes such as lymphoblastic lymphoma and Burkitt’s lymphomas systemically received CNS prophylaxis because of the well known propensity of these lymphomas to involve the CNS. In contrast, the risk of meningeal involvement from unstratified low-grade NHL is low, and CNS prophylaxis is generally not recommended.2,12 Controversy on CNS prophylaxis is open in other aggressive lymphomas, especially diffuse large B-cell lymphomas (DLBCL), in which no consensus on CNS prophylaxis in specific situations has been reached. On the other hand, the new diagnostic tools for the detection of meningeal involvement, such as flow cytometry of cerebrospinal fluid (CSF), have led to the detection of a greater number of patients with occult CNS disease compared to conventional cytology.2,11,12 In some of these studies, patients with occult CNS disease showed a trend to high-risk of NHL relapse.11 In addition to this poorly clarified situation, and contrary to the proven efficacy of CNS prophylaxis in patients with acute
lymphoblastic leukemia (ALL), conclusions regarding the efficacy of CNS prophylaxis on CNS disease remain controversial in some studies.11,12. This is mainly due to the heterogeneity in drugs and schedules administered, the small number of patients and/or the lack of a control arm in most studies. Besides the heterogeneity for indications of CNS prophylaxis, schedules of prophylaxis and treatment of CNS involvement in NHL homogeneous in different countries are lacking, even within the same country, and have been scarcely investigated.4,13. The QUIT (Registro Español de Pacientes que Reciben Quimioterapia intratratamental) registry was an initiative of the PETHEMA (Programa Español de Tratamiento de las Hemopatías Malignas, Asociación Española de Hematología y Hemoterapia), GELTAMO (Grupo Español de Linfomas/Trasplante Autólogo de Médula Ossea) and GOTEL (Grupo Oncológico para el Tratamiento y Estudio de los Linfomas) groups designed to prospectively know the current practice of CNS prophylaxis and therapy in patients diagnosed with hematological malignancies (acute leukemias [AL] and lymphoproliferative disorders) in Spain. The results in ALL patients have recently been reported14. The objective of this study was to report the practice of CNS prophylaxis and treatment in patients with lymphoproliferative disorders.

Patients and methods

The QUIT study was presented at meetings of the Spanish PETHEMA, GELTAMO and GOTEL groups to select participating hospitals as has been previously described16. Briefly, from June 2005 to June 2006 all patients (≥18 years old) diagnosed with ALL or other lymphoproliferative disorders who received CNS prophylaxis or CNS treatment were consecutively included through online registration in 33 hospitals. Each patient was included only once. The questionnaire included sociodemographic variables (age, sex, hospital), NHL subtype (or type of lymphoproliferative disorder at time of diagnosis, stage [Ann Arbor], International Prognostic Index [IPI] score)17.

With regard to meningeal involvement, the timing of the CNS involvement (at diagnosis or at relapse), date of diagnosis of neoplastic meningeal or intracranial symptoms at the time of CNS involvement (including headache, nausea and vomiting, mental status abnormalities, cranial nerve signs, visual disorders, intracranial hypertension [after and during IT therapy] as well as focal neurological signs, alteration of consciousness and CSF pleocytosis) were recorded. The following data of CNS therapy were recorded: regimen of CNS-directed therapy (prophylaxis or treatment, and in the case of the prophylaxis, the nucleoside analogue schedule, extrathecal administration [1 or ≥2]; site of extrathecal involvement, raised LDH, age > 60, bone marrow involvement, bulky mass, interstitial neuropathy in 7, loss of vision in 6 and seizures in 1.

As can be observed in table 3, the most common CNS-directed therapy reported in cases with CNS involvement was IT, although it is of note that a little half of the patients were treated with IT depot liposomal cytarabine. Regarding IT administration schedule, in most of the cases (<15) IT therapy was administered every 15 days (to almost all the patients corresponding to those receiving IT depot liposomal cytarabine) or 2-3 times weekly, whereas lumbar puncture was the preferred route for IT administration (37 out of the 41 patients). Cranial irradiation was used in 4 cases (local radiotherapy in 3 and craniospinal radiotherapy in the remaining).

In the group of patients who received CNS prophylaxis (n = 187), IT was also the most frequent schedule (table 3), and in fact, only three patients received IT depot liposomal cytarabine as CNS prophylaxis. Two patients diagnosed with DLBCL (one with elevated median high IPI score, and others), date of the onset of IT therapy (methotrexate [MTX], cytarabine, triple therapy [including MTX, cytarabine and hydrocortisone]), route (IT through lumbar puncture or intraventricular) and schedule of administration, as well as the other CNS-directed therapies such as cranial irradiation (for the use of radiotherapy).

Results

A total of 228 patients diagnosed with lymphoproliferative disorders from 33 hospitals were included. The mean (standard deviation [SD]) age was 52 (± 16) yr. (range 18-83), with 63 (34%) patients older than 60 years, and 144 (63%) males. DLBCL was the most frequent histologic subtype (133 patients [58%]), followed by Burkitt’s lymphoma (37 patients [16%]) and MCL (11 cases [4.8%]). Table 1 provides a complete list of the lymphoproliferative disorders. At the time of diagnosis, half of the patients presented with B symptoms and three quarters had advanced disease (stage IV in 149 [65%]). A total of 228 patients (79%) showed extranodal involvement, being bone marrow the most frequent extranodal site involved (81 patients) followed by CNS, liver and lung (30 cases each one). The LDH level was increased in 63% of the cases and 62% had an IPI score higher than 2. The main demographic and clinical characteristics are listed in table 2.

IT therapy was administered for neoplastic meningitis in 41 cases, and CNS prophylaxis in 187. Thirty out of 41 patients showed CNS involvement at the time of diagnosis of lymphoproliferative disorders, whereas 11 showed CNS relapse. Diagnosis of CNS involvement was established by the observation of malignant cells in CSF in 33 cases, with a median of cell count of 18 cells/μl (range 2-1000), or by imaging techniques (MRI in 15 and CT scan in 8). In 17 patients (41%) CSF involvement was confirmed by flow cytometry. Neurological symptoms included: impairment in March, headache in 17, mental status impairment in 14 cases, cranial nerve palsy in 14, muscle weakness in 12, nausea and vomiting in 10, diplopia in 9, sensorial neuropathy in 7, loss of vision in 6 and seizures in 1.

B-Cell neoplasms (n = 218 [95%])

- Precursor B-cell neoplasm 4
- B-cell chronic lymphocytic leukemia, small lymphocytic lymphoma 5
- Mantle-cell lymphoma 11
- Follicular lymphoma 8
- Extramedullary marginal zone B-cell lymphoma 3
- Splenic marginal zone B-cell lymphoma 1
- Mantle-cell lymphoma 1
- Diffuse large B-cell lymphoma 136
- Burkitt’s lymphoma 37
- T-cell and NK-cell neoplasms (n = 22 [10%])
- Precursor T-cell neoplasm 8
- T-cell prolymphocytic leukemia 1
- Extranodal NK T-cell lymphoma, nasal type 3
- Intergrowth T-cell/LTCL 1
- Peripheral T-cell lymphoma unspecified 1

TABLE 1

Lymphoproliferative disorders according to the World Health Organisation classification included in the QUIT registry

n
B-Cell neoplasms (n = 218 [95%])

- Precursor B-cell neoplasm 4
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- Intergrowth T-cell/LTCL 1
- Peripheral T-cell lymphoma unspecified 1
- Total
Histologic subtypes. 

Intrathecal and other central nervous system directed therapies used in patients diagnosed with lymphoproliferative disorders included in the QUIT registry

<table>
<thead>
<tr>
<th>Variables</th>
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<th>CNS prophylaxis (%)</th>
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<td>&gt; 60</td>
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<td>56</td>
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Discussion

Similar to a previous study by our group focused on CNS prophylaxis and therapy for AL patients, this is the first study that prospectively describes the current practice of prophylaxis and therapy for neoplastic meningitis by lymphomas and other lymphoproliferative disorders in Spain. As observed in AL study, the most frequent therapy for CNS involvement or CNS prophylaxis was TIT, and lumbar puncture was the preferred route for IT administration. The introduction of new drugs, especially liposomal depot cytarabine for therapy of CNS infiltration and the scarce use of radiotherapy are also of note. On the other hand, and conversely to patients with AL, one of the most relevant findings of this study was the marked differences between investigators in the indications of CNS prophylaxis for most of the cases, reflecting the disparity in criteria for CNS prophylaxis, a feature also described in other studies.

In most of the studies on the risk of CNS relapse in patients with lymphoma, the histologic subtype has been indicated as one of the main risk factors. Thus, there is a consensus on the need of CNS-directed therapy in some aggressive lymphomas such as BURKitt’s lymphoma and lymphoblastic lymphoma, in which the risk of CNS relapse in the absence of prophylaxis could achieve 20%-25%. However, the risk of CNS relapse in the untransformed low-grade lymphomas is low, and there is no evidence for the routine use of CNS prophylaxis, with the exception of high-grade transformation. However, 10 patients diagnosed with follicular or marginal zone lymphomas in the QUIT registry received IT prophylaxis, mostly due to the presence of other risk factors for CNS disease identified in studies focused on aggressive NHL (table 4).

The controversy in the criteria used for CNS prophylaxis especially arises in other aggressive lymphomas such as the blastoid variant of MCL, anaplastic large cell lymphoma, peripheral T cell lymphomas and, especially, DLBCL. Case-series studies have estimated that the risk of CNS relapse for patients diagnosed with DLBCL is about 5% to 14%. The use of systematic prophylaxis in these cases could lead to the treatment of patients who may never have CNS relapse. For this reason, many of these studies have tried to identify which of these patients are at risk of developing CNS disease based on the presence of other risk factors. One of the largest studies is that by Hollenber et al. in which more than 2,500 patients diagnosed with NHL were studied for the incidence and risk factors for CNS disease. These authors described a score system based on the findings of five independent risk factors: raised serum LDH level, serum albumin over 35 g/L, age less than 60 yr, retroperitoneal lymph node involvement, and involvement of more than one extranodal site. The presence of 4 or 5 of these factors increased the risk of CNS recurrence by 25%. In the study by Haasen et al., the risk of CNS relapse increased in patients with raised LDH or with involvement of more than one extranodal site, although when IPI was added to multivariate analysis it remained as the only parameter with statistical significance, identical to the report by Feugier et al. In a recent article, increased serum LDH level or involvement of more than one extranodal site.
sis12. In this sense, the guidelines of the
difficult to detect by multivariate analy-
cance of this increased involvement is
444 Med Clin (Barc). 2008;131(12):441-6
of anatomical sites associated, in some
prophylaxis in patients with involvement
probably reflects the trend to use CNS
rementioned studies. In fact, this finding
some findings were of note. The first is
relapse.
Risk factors associated with higher CNS
one extranodal site were, again, the main
risk factors associated with higher CNS
relapse.
Although many patients with DLBCL in-
cluded in the QUIT registry received CNS
prophylaxis according to some of the
above mentioned reasons (raised LDH
levels and intermediate-high IPI score),
some findings were of note. The first is
that the main criteria for CNS prophylaxis
was the presence of only one extranodal
site in 55 patients with this histologic
subtype, a risk factor not cited in the af-
fermented studies. In fact, this finding
probably reflects the trend to use CNS
prophylaxis in patients with involvement
of anatomical sites associated, in some
studies, with a higher risk of CNS involve-
ment, such as bone marrow, paraaortic
sinuses24, breast23, epidural space24 or
testicular involvement25-28, yet the signifi-
cance of this increased involvement is
difficult to detect by multivariate anal-
ysis21. In this sense, the guidelines of the
National Comprehensive Cancer Network
(NCCN)29 recommend CNS prophylaxis in
patients with DLBCL and involvement
of these mentioned sites. Identical results
to those of our study were observed in sim-
ilar studies conducted in the UK30 and
Canada18, in which only a minority of cli-
nicians used a high IPI score, increased
erase LDH level or more than one extra-
nodal site as criteria for CNS prophylaxis.
The second remarkable finding in our
study is that bulky disease was also men-
tioned as a reason for CNS prophylaxis in
24 patients with DLBCL. Bulky disease
has not been associated with a high-risk
of CNS involvement and, in fact, in the
study by Tomita et al31 CNS relapse was
observed more frequently in the group of
patients with less frequency of bulky
masses. Third, HIV infection was inclu-
ded as a reason for CNS prophylaxis in
32 cases (12 diagnosed with DLBCL).
CNS prophylaxis should be administered
only for aggressi-
ve lymphomas or bone marrow involve-
ment. In addition, in one study36, the
frequency of CNS involvement had signi-
cantly decreased in patients with HIV-
related lymphomas who were receiving
highly active antiretroviral therapy (HA-
ART). Finally, although a high risk of CNS
disease has been associated with youn-
ger age148,28, in our study age over 60 yr
was included as criteria for CNS prophyl-
axis in 28 patients (23 diagnosed with
DLBCL), probably reflecting the fact that
advanced age is a risk factor included in
the IPI score.
As described for patients diagnosed with
ALL29, there was a massive use of TIT as
the preferred schedule for CNS prophyla-
xis, conversely to reports in other foreign
studies in which IT MTX alone or combi-
ned with soluble steroids was the most
frequent IT therapy26,27,31. The reason has
been previously discussed29 and was
a consequence of the wide use of the
risk-adapted protocols from the PETHIE-
MA group in Spain for treatment of pa-
tients with ALL. Burkitt’s and lymphoblas-
tic lymphoma, that could exert a mimetic
effect leading to a generalization of this
schedule for CNS prophylaxis for the re-
main ing lymphoid malignancies.
Another remarkable feature of the QUIT
study was the administration of IT depot
liposomal cytarabine in almost 50% of
the cases of lymphomas with CNS invol-
vement. Due to its long half time in CSF,
IT depot liposomal cytarabine can be ad-
ministered every two weeks, allowing fe-
ner IT administrations36,37. The efficacy of
this drug in lymphomatous meningeosis
has been established in several stud-
ies38-40, and it indeed constitutes an ac-
cepted indication by the regulatory agen-
cies. It is noted, however, that 3 patients
also received IT depot liposomal c~tarabi-
ne as CNS prophylaxis despite the scarce
information available in this setting. Mc
Clune et al40 included 14 patients with
ALL or high-grade non-Hodgkin’s lymp-
	
TABLE 4

Reasons most frequently cited for central nervous system prophylaxis by the main histologic subtypes

<table>
<thead>
<tr>
<th>Histology</th>
<th>n</th>
<th>Reasons for CNS prophylaxis</th>
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<td>Extramedial involvement</td>
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<td></td>
<td>Increased LDH</td>
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<td></td>
<td>Intermediate-high IPI score</td>
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<tr>
<td></td>
<td></td>
<td>Bulky disease</td>
<td>24</td>
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<tr>
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<td></td>
<td>Age &gt; 60 yr</td>
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<td></td>
<td></td>
<td>Extramedial involvement ≥ 2</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>HIV infection</td>
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<td>Burkitt’s lymphoma</td>
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<td>Bulky disease</td>
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*Patients are from more than one registry for CNS prophylaxis.

CNS - central nervous system; DLBCL - diffuse large B cell lymphoma; HIV - human immunodeficiency virus; IPI - International Prognostic Index; LDH - lactate dehydrogenase; SCT - stem cell transplantation.
more frequent CSF involvement compared to conventional cytology. In a recent study by Hedge et al., the detection of CSF by flow cytometry was associated with the presence of more than one extranodal site, in contrast to the main risk factors for CNS relapse reported in several studies, suggesting that patients with CNS involvement detected by cytometry could be at risk for meningeal relapse. In addition, among the patients with evidence of occult CSF lymphoma by flow cytometry, CNS relapse was observed in 10% vs. 16% in patients with negative CSF flow cytometry. It is of note, however, that this technique is not currently accepted as standard for CNS involvement detection, but could become a standard procedure in the future. The lack of the systematic inclusion of all the cases in which CNS-directed therapy was administered constitutes the main limitation of the present study. However, the design of this survey (cross-sectional and consecutive) and the similar results obtained in other surveys conducted in foreign countries indicate that this registry probably was a representative sample of the practice of CNS prophylaxis and treatment in patients with lymphoproliferative disorders in Spain. In conclusion, the results of this study point out the generalized use of IT therapeutic regimens in patients with NHL and other lymphoproliferative disorders, as well as the increasing use of new formulations of drugs, such as IT dexamethasone, prednisolone, rituximab, and the scarce use of radiotherapy. It is possible that the results of this study can serve as an example of the practice of CNS prophylaxis in some aggressive lymphomas, especially DLBCL, of is of note.

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