Practice guidelines for the management of extranodal non-Hodgkin's lymphomas of adult non-immunodeficient patients. Part I: primary lung and mediastinal lymphomas. A project of the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation

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ABSTRACT

Extranodal non-Hodgkin's lymphomas constitute 20-25% of overall non-Hodgkin's lymphomas cases and can be managed with very different therapeutic strategies. Therefore, the Italian Society of Hematology and the two affiliate societies (the Italian Society of Experimental Hematology and the Italian Group of Bone Marrow Transplantation) appointed a panel of experts to produce clinical practice-guidelines for the management of these conditions. Primary lung and mediastinal lymphomas were the objective of this part of the project. The panel of experts produced the following key recommendations that were graded according to the strength of evidence and clinical judgement. The first-line therapy for non-MALT primary lung non-Hodgkin's lymphomas should include anthracycline-based chemotherapy with CHOP or CHOP-like, MACOP-B or MACOP-B-like regimens (grade D). Rituximab association with chemotherapy needs to be evaluated within approved clinical trials. Second-line therapy with high-dose chemotherapy and autologous stem cell transplantation is recommended (grade B). In patients with MALT primary lung non-Hodgkin's lymphomas, the recommended first-line therapy should include chlorambucil, CHOP, CHOP-like or fludarabine-containing regimens (grade B). Radiotherapy is to be reserved for patients with a unique, small lesion in a poorly mobile site and with contraindication to surgery (grade D). Rituximab should be administered only within approved clinical trials. For treatment of primary mediastinal large B-cell lymphomas, the recommended first-line therapy is a chemotherapy and radiotherapy association (grade B). An anthracycline-based chemotherapy with CHOP, MACOP-B or VACOP-B is recommended (grade B). Rituximab combination with chemotherapy is highly suggested but only for patients enrolled into approved clinical trials. Patients with an inadequate early response should be candidates for early intensification with high-dose chemotherapy (grade C). Patients with refractory or relapsed disease should undergo rescue programs including intensive, non-cross-resistant debulking treatment followed, in chemosensitive patients, by high-dose chemotherapy and autologous stem cell transplantation (grade B).

Key words: non-Hodgkin's lymphoma, clinical practice guidelines, systematic review, chemotherapy.

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Introduction

In order to reserve patients for the best available treatments and avoid the risk of inappropriate therapies, since 2001 the Italian Society of Hematology (SIE) has been supporting the development of clinical practice guidelines in the therapy of selected hematologic malignancies. The Italian Society of Experimental Hematology (SIES) and the Italian Group for Bone Marrow Transplantation (GITMO) have since then shared this aim. We present the first part of a project aimed at producing recommendations for extranodal non-Hodgkin's lymphoma (NHL), dedicated to lung and mediastinal primary NHL. The guidelines are intended to support the clinical practice of hematologists, oncologists and internists who care for lymphoma patients.

Design and Methods

The methodology for developing SIE guidelines has been extensively reported elsewhere.[1] Eight senior hematologists (the expert panel) and two literature reviewers composed the working group. During the first meeting, the areas of major concern in the management of extranodal NHL were selected by generating and rank-ordering clinical key-questions using the criterion of clinical relevance, i.e. impact on the management of patients and risk of inappropriateness, through a Delphi process.[2] The clinical domains and the key-questions that ranked highest formed the set of topics of the present guidelines.

The evidence base was built through systematic search of common medical literature databases for relevant papers published up to March 2007. The search was updated in January 2008. The proceedings of ASH 2003-2007, ASCO 2003-2007, and EHA 2003-2007 were scanned for relevant abstracts. Finally, the major hematology, oncology and general medicine journals (*Blood, Journal of Clinical Oncology, British Journal of Hematology, Bone Marrow Transplantation, Haematologica, New England Journal of Medicine, Lancet*) were manually searched for relevant papers published from 1995. The full reference list (including the abstracts of full papers) is available on request from *marchettim@smatteo.pv.it*. Full papers were assigned an evidence level, according to the Scottish Intercollegiate Guideline Network.[3] Based on the retrieved literature, the expert panel formulated evidence-based recommendations. Judgment-based recommendations were formulated by the use of consensus methodologies when relevant areas could not be addressed by the available evidence. A first round of consensus for the proposed recommendations was obtained through paper questionnaires, according to the Delphi technique.[2] Nominal group technique[4] was used for the final recommendation statements. The guidelines were reported according to the COGS checklist by the Conference on Guideline Standardization.[5]

Updating of the present guidelines is due in 2011.

Definitions

The present guidelines apply to patients with lung and mediastinal primary lymphomas. The guidelines do not apply to patients with acquired immunodeficiency sustained by HIV or anti-graft immunosuppressive agents (post-transplant lymphoproliferative disorders).

The expert panel agreed on the use of the Ann Arbor staging system as modified by the Cotswolds meeting.[6] Standard definitions for complete response (CR), complete response untested (CRu), and partial remission (PR) were adopted. An operational definition of elderly patients was considered throughout the text that takes into account not only age but also performance status and comorbidities.

Results

Primary lung lymphomas

Primary pulmonary lymphomas are clonal lymphoid processes involving mainly the lung parenchyma and/or large airways without extension to the extrapulmonary sites at the diagnosis or during the three months after the diagnosis. Hilar or mediastinal lymphnodes may be enlarged but the neoplastic burden is more evident in the lung tissue.[8] The most common type of primary pulmonary lymphoma is marginal zone B-cell lymphoma, which arises from bronchus-associated lymphoid tissue, and represents 70-90% of all primary pulmonary lymphomas.[8] The translocation t(11;18)(q21;q21), which results in a fusion of the cIAP2 region on chromosome 11q21 with the *MALT1* gene on chromosome 18q21, is documented in more than one-third of cases.[9] Diffuse large-B-cell lymphomas make up 10% of cases of primary pulmonary lymphomas,[8] and the lung is the most common site of involvement of lymphomatoid granulomatosis, an angiocentric and angiodestructive lymphoproliferative disease.[10-12]

No paper comparing different procedures for initial staging work-up in patients with lung lymphoma was found. Therefore, the panel gave recommendations on the use of specific investigations according to a good clinical practice principle. In particular, the panel agreed to include in staging primary lung lymphoma those tests previously recommended for nodal diffuse large B-cell lymphomas (DLBCL).[1]

The panel explicitly discussed the decision options for first-line therapy for the NHL of the lung. Options were restricted between the following therapeutic strategies: *watch and wait* approach, surgery, chemotherapy and chemotherapy followed by radiotherapy.

No comparative studies analyzed separately the *watch and wait* option. One retrospective cohort analysis (evidence level 3) reported 11 patients with MALT lymphoma of the lung who did not undergo treatment following initial diagnosis.[13] The median time of observation without therapy was 28.1 months. Within this time, all 11 patients showed at least stable disease. Six of these 11 patients, however, had spontaneous regressions and *wax and wane* phenomena of the pulmonary lesions, but not of extrapulmonary manifestations. One patient was referred for treatment after progression in

Table 1. Case series including cases of primary pulmonary MALT lymphomas.

	Number of patients	*Lung surgical resection*	*Chemotherapy*	*Rituximab*	*Radiotherapy*	*CR/PR*	*5 yr OS % (10 yr OS)*	*5 yr RFS %*
Koss *et al.*, 1983[14]	44	NR	NR	NR	NR	NR	95 (85)	NR
Kennedy *et al.*, 1985[15]	32	10	18	NR	NR	NR	90 (78)	NR
Li *et al.*, 1990[16]	33	14	14	NR	5	NR	85 (75)	<54
Cordier *et al.*, 1995[17]	64	42	18	NR	5	NR	94 (50)	NR
Fiche *et al.*, 1995[18]	69	46	20	NR	6	NR	93.6% in low grades	NR
Wislez *et al.*, 1999[19]	13	3	10	NR	NR	7/5	100	NR
Ferraro *et al.*, 2000[20]	35	19	26	NR	2	NR	68 (53)	NR
Kurtin *et al.*, 2001[21]	50	NR	NR	NR	NR	NR	85 (72)	NR
Zinzani *et al.*, 2003[22]	12	4	10	NR	NR	12/0	100	>50
Zucca *et al.*, 2003[23]	15	NR	NR	NR	NR	NR	100	75
Ahmed *et al.*, 2004[24]	22	6	10	10	2	9/10	<100	<60
Graham *et al.*, 2005[25]	17	6	8	1	NR	NR	82%	NR

NR: not reported.

the lung, while two patients experienced progression outside the lung. This study suggests that MALT lymphoma of the lung is a very indolent disease with the potential for spontaneous regression. The panel agreed that patients diagnosed with pulmonary MALT lymphoma might not require immediate treatment in the absence of symptoms and a *watch and wait* policy could be adopted.

As direct evidence for initial treatment, the expert panel considered 13 non-comparative, cohort studies, dealing with small and heterogeneous series of patients with lung lymphoma (level of evidence 3) (Table 1).[14-25] Two outcome studies,[26,27] and 3 phase II intervention studies dealing with MALT lymphomas (level of evidence 3)[28-30] were also analyzed as translated evidence. Early studies suggested that radical operation could be considered the definitive therapeutic maneuver. Ferraro *et al*. in 48 patients who underwent surgery for primary pulmonary non-Hodgkin's lymphoma [males 21 (44%); females 27 (56%); mean age 61.8 yrs; asymptomatic 37.5%; MALT type 35 (73%); non-MALT type 13 (27%)] obtained a complete resection in 19 cases (40%).[20] In patients with MALT type lymphoma the overall survival at one year was 91%, the overall survival at five years was 68% and the overall survival at ten years was 53%. These data were weighted taking into account the fact that this lymphoma is an indolent disease usually with a long natural course, and that it is a multifocal disease in which a radical resection is not easy to perform. Furthermore, lung surgery is not without risks since thoracic pain and lung function impairment have been observed in about 10-15% of cases. Radiotherapy alone with a total dose of 30-35 Gy in 15-20 fractions (3-4 weeks) has been showed to guarantee a low failure-free rate in MALT lymphomas.[26] However, in patients with primary pulmonary lymphomas of MALT type the results were not as good as in the whole population of MALT lymphomas; this may be explained by the fact that lungs are mobile organs.[26] Chemotherapy with anthracyclines or combined modality therapy mainly with a CHOP regimen, was associated with a 10-year lymphoma specific survival of 72% in a study on 50 patients.[21] In this study no differences in survival were seen between subjects with low grade MALT lymphoma and patients in which MALT lymphoma was associated to areas of large B-cell lymphoma. Zinzani *et al.*[27] reported a series in which patients received either fludarabine/mitoxantrone (FM) or cyclophosphamide, vincristine and prednisone (CVP). Twenty patients were treated with the FM regimen (25 mg/m^2 per day fludarabine on days 1–3 and 10 mg/m^2 mitoxantrone on day 1 only), 11 patients were treated with the CVP regimen (400 mg/m^2 per day cyclophosphamide on days 1–5, mg/m^2 vincristine on day 1, and prednisone). In both regimens, courses were administered at 3-week intervals for a total of 6 cycles. The recurrence free survival rate was almost 100 % at 60 months.

Regarding the role of rituximab in primary pulmonary lymphoma of MALT type, so far there are only a few case reports with conflicting results.[31-33]

Due to the absence of comparative studies, the panel provided recommendations based mostly on consensus formation techniques and according to a good clinical practice principle (grade D).

Recommendations

Patients with non-MALT primary lung NHL need pre-treatment evaluation as for nodal diffuse large B-cell lymphomas (DLBCL) plus specific investigations including bronchoscopy, thorax and abdomen CT scan with high-resolution CT scan of the thorax, and pulmonary function tests including transfer capacity for carbon monoxide (TLCO) (grade D).

Surgical resection is not required for debulking aims, but can be requested for atelectasiae.

The recommended first-line therapy includes anthracycline-based chemotherapy with CHOP or CHOP-like, MACOP-B or MACOP-B-like regimens (grade B).

Rituximab association with chemotherapy needs to be evaluated within approved clinical trials.

Response should be evaluated as for nodal DLBCL, including pulmonary function tests (grade D).

Follow-up should be conducted as for nodal DLBCL, including pulmonary function tests (grade D).

As for nodal DLBCL, second-line therapy with high-dose chemotherapy and autologous SCT is recommended (grade B).

Patients with MALT primary lung NHL need pre-treatment evaluation including bronchoscopy, thorax and abdomen CT scan with high-resolution CT scan of the thorax, pulmonary function tests including TLCO, bone marrow biopsy, immunoelectrophoresis, LDH, β-2-microglobulin.

Patients with localized MALT primary lung NHL without symptoms should be managed with a "watch and wait" approach (grade D).

Surgery is not recommended for pre-treatment evaluation but it can be performed in patients with localized disease, whenever a wedge resection or middle lobe and lingula excision are possible (grade D).

The recommended first-line therapy should include chlorambucil, CHOP, CHOP-like or fludarabine-containing regimens (grade B).

Radiotherapy is to be reserved for patients with a unique, small lesion in a poorly mobile site and with counterindication to surgery (grade D).

Rituximab should be administered only within approved clinical trials.

Post-treatment evaluation and follow-up of patients with complete remission should follow the guidelines for nodal indolent NHL, including also high-resolution CT of the thorax, pulmonary function tests with TLCO (grade D).

Primary mediastinal large B-cell lymphomas

Primary mediastinal large B-cell lymphoma (PMLBCL) is a diffuse large B-cell lymphoma that arises in the thymus and is considered a peripheral B-cell neoplasm. Table 2 summarizes the clinical comparison of diffuse large B-cell lymphoma and PMLBCL. In a review of cases of non-Hodgkin's lymphomas (NHL) from 9 centers all over the world, PMLBCL was found to account for 2%.[34] Molecular analysis and gene expression profiling have identified PMBCL as a distinct and more favorable subgroup of DLBCL.[35-37] Using array-based comparative genomic hybridization, candidates genes were selected in the context of NF-κB transcription activation, human leukocyte antigen class I/II defects, impaired apoptosis and Janus kinase/signal transducer and activator of transcription (JAK/STAT) activation.[38] These data confirm the genomic uniqueness of this tumor. PMLBCL appears to be a distinct clinicopathological entity, characterized by locally invasive anterior mediastinal mass with notable aggressiveness. The mass frequently compromises the airway, determining a superior vena cava syndrome.[39] At the time of diagnosis, stage of disease is I-II in 80% of the patients. Mediastinal tumor is larger than 10 cm (bulky mass) in 60-70% of patients, infiltrating lung, chest wall, pleura, and pericardium. Pleural or pericardial effusions are present in one-third of cases. The invasive neoplasm results in cough, chest pain, dyspnea, or complaints resulting from caval obstruction. Spread to peripheral lymph nodes is infrequent, and marrow or cerebrospinal fluid involvement unusual. Distant relapses tend to be extranodal, including liver, gastrointestinal tract, kidneys, ovaries, adrenal glands, pancreas, or central nervous system.[40]

Table 2. Comparison of DLBCL and PMLBCL.

	DLBCL	*PMLBCL*
Median age (years)	55	35
Nodal/extranodal presentation	65%/35%	0%/100%
Sex distribution (M:F)	1:1	1:4
Stage I-II/III-IV	40%/60%	80%/20%
Bulky disease	30%	60%-70%

Staging

No specific paper comparing different procedures in patients with PMLBCL for initial staging work-up was found. Outcome studies reporting Gallium[67] scanning (^{67}GaSPECT) procedure for staging, response and relapse assessment and follow-up were analyzed.[41-43] ^{18}FDG-PET was shown to be extremely useful for the assessment of residual masses considering the elevated tracer uptake that characterizes this lymphoma, but a longer experience is necessary. Thus, the panel produced recommendations on the use of staging procedures according to a good clinical practice principle.

Chemotherapy

Outcome or phase II non-comparative studies in mediastinal lymphomas (evidence grade 3) reported the results of approaches with first-generation[44-53] to third-generation[34,40,42,54-60] chemotherapy protocols. One comparative study (evidence grade II) analyzing the use of different chemotherapeutic regimens (CHOP or CHOP-like *vs.* third-generation regimens) for advanced non-Hodgkin's lymphoma was used as indirect evidence.[61] Early studies suggesting that PMLBCL were unusually aggressive with a poorer prognosis with respect to other large-cell lymphomas have been contradicted by more recent reports. Complete response (CR) rates of 53-80% have been reported after initial therapy with a 50-65% overall survival rate at five years. The comparative study showed that CHOP and intensive third-generation regimens produce equivalent results.[61] Several European centers have suggested that MACOP-B regimen may be superior to CHOP regimen.[43,55-57,59] However, the panel claimed it was difficult to compare the different types of protocols and to explain the rather different CR and survival rates reported by different institutions using similar regimens. Phase II studies were judged to have been potentially influenced by patient selection bias. Considering the published phase II data by centers that have used both first-generation chemotherapy regimens like CHOP and other more aggressive third-generation ones like MACOP-B, the results clearly favored the latter. Todeschini *et al.*[57] used CHOP in 6 patients with mediastinal lymphoma without achieving a single CR. Lazzarino *et al.*[55] treated 30 patients: the CR rate after CHOP was 36%, while that after MACOP-B or VACOP-B was 73%. In a multicenter study of 106 patients, the 3-year relapse-free survival (RFS) was 38% in the 47 patients treated with CHOP and 58% in the 62 patients treated with MACOP-B or

VACOP-B.[40] In 2 previous studies,[43,59] Zinzani *et al*. used MACOP-B regimen in 50 patients (a two-center prospective trial) and in 89 patients (an Italian multicenter prospective trial) respectively: the CR rates were 86% and 88% respectively, while the 5-year RFS rates were 93% and 91% respectively. A retrospective International Extranodal Lymphoma Study Group (IELSG) study of 426 patients with PMLBCL confirmed the superiority of the third-generation chemotherapy strategies over first-generation ones in terms of survival.[62] In addition, the same results have been reported by Todeschini *et al*.[63] in a retrospective study.

The panel analyzed 3 outcome studies (evidence grade 3) dealing with the use of high-dose approaches including autologous stem cell transplantation and high-dose sequential treatment. The data do not prove superiority of high-dose chemotherapy over conventional chemotherapy.[64-66] The use of high-dose chemotherapy supported by stem cell transplantation to consolidate the initial response in high-risk patients resulted inconclusive.

Radiation therapy

The issue of adjuvant radiation therapy after chemotherapy remains open. The excellent results obtained in the GELA study[34] without radiation therapy have questioned its necessity. The panel considered 2 outcome analyses from two recent Italian studies,[43,59] indicating that the addition of radiation therapy after chemotherapy is of pivotal importance for the eradication of PMLBCL in terms of increasing the CR rate or reinforcing existing CRs after induction chemotherapy. In particular, 70% of the patients had residual mediastinal tumor masses after chemotherapy (MACOP-B) according to the first report,[43] while it was 44% after radiation therapy. Sixty-six percent of the patients showed persistent abnormal uptake at 67Ga SPECT after MACOP-B, while following radiation therapy, 19% of the patients were still 67Ga SPECT positive. In the second study,[59] after the chemotherapy regimen (MACOP-B), 26% of the patients achieved a CR and 66% obtained a partial response (PR), giving an overall response rate of 92%. After radiation therapy, 93% of the patients who had already achieved a PR obtained CR status. So, after the combined modality treatment, 88% of the patients achieved a CR.

Rituximab

Regarding the role of rituximab in PMLBCL treatment, 4 observational and one phase II trials were analyzed by the panel.[67-70] A statistically significant advantage for the combination of rituximab plus DA-EPOCH was observed in one study,[67] and an increase in terms of complete response, failure-free survival, and overall survival for the CHOP plus rituximab versus CHOP alone was reported in another.[68] In the latter study, the data obtained with the combined treatment was equivalent to the previously published MACOP-B/VACOP-B data without rituximab. The preliminary data of an Italian experience with MACOP-B plus rituximab achieved comparable results when analyzing the historical MACOP-B/VACOP-B alone data.[69] Furthermore, in a retrospective study Savage *et al*.[70] showed that patients treated with CHOP plus rituximab obtained the same results in terms of 5-year overall survival as with MACOP-B/VACOP-B patients. The panel considered the evidence in favor of rituximab inclusive and further randomized studies should consider the impact on these comparisons. Recently, the International Extranodal Lymphoma Study Group has started a trial comparing first generation chemotherapy versus third generation chemotherapy in association with rituximab.

Restaging

Several patients with PMLBCL have residual radiographic abnormalities in the mediastinum even after CR, so chest X-ray and CT scans do not provide a valid basis for therapeutic decision making. ^{67}Ga SPECT could be the best tool for selecting those patients who really require the addition of radiation therapy after chemotherapeutic induction. In an observational (evidence grade 3) study,[43] 60% of the patients with positive ^{67}Ga SPECT and negative CT scan relapsed after combined modality treatment, while no relapses were observed with negative ^{67}Ga SPECT and CT scan. This restaging method allows identification of a subset of patients with residual radiographic abnormalities who need no further therapy (negative ^{67}Ga SPECT) and of poor prognosis patients who do require further treatment.

Recurrent disease

Generally, patients with PMLBCL who obtain a CR lasting longer than 18-24 months after diagnosis are likely to be cured. In fact, most relapses occur within the first 12 months after the completion of the front-line treatment. A standard therapeutic option for patients with relapsed disease has not yet been identified. Considering the young age of these patients and the pattern of relapse which spares the bone marrow, high-dose chemotherapy supported by autologous stem cell transplantation has been tested in 2 observational outcome studies (grade of evidence 3) as rescue therapy.[65,66] With this strategy, relapsed mediastinal lymphomas seem to have a better prognosis with respect to the other diffuse large cell lymphoma, with a 5-year disease-free survival of 55% and 35% respectively. In contrast, patients treated with a conventional second-line chemotherapy or with radiation therapy on the mediastinum (for patients who did not undergo radiation therapy after the front-line chemotherapy regimen) have a median survival after relapse of a few months.

Recommendations

Staging work-up for primary mediastinal DLBCL should be the same as for nodal DLBCL, but should also include chest X-ray and PET scanning (grade D). As for nodal DLBCL, a lumbar puncture with examination of cerebrovascular fluid is recommended for those patients who have a high risk of CNS involvement, such as those with an increased LDH level associated with extranodal disease such as suprarenal, renal, liver or ovary involvement (grade D).

The recommended first-line therapy is a chemotherapy and radiotherapy association (grade B).

An anthracycline-based chemotherapy with CHOP, MACOP-B or VACOP-B is recommended (grade B).

Mediastinal RT should start within eight weeks from the last dose of chemotherapy. A dose of at least 30 Gy should be delivered to the original tumor volume (grade B).

Rituximab combination with chemotherapy is strongly suggested but only for patients enrolled into approved clinical trials (grade C).

Patients should receive an early evaluation with CT scan during the first courses of chemotherapy (about half-way through the programed courses) in order to identify patients with inadequate response, i.e. less than partial response (grade D).

Patients with an inadequate early response should be candidates for early intensification with high-dose chemotherapy (grade C).

At the end of chemotherapy, patients should be evaluated with CT scan and PET, in order to assess a progression which occurred in the second half of the chemotherapy period (grade D).

Patients should be ultimately evaluated at least 4-12 weeks after the end of radiotherapy as for nodal DLBCL, i.e. including CT scan and PET scan (grade D).

No definite recommendation can be currently formulated for patients without a bulky disease who achieve a PET-negative state at the end of chemotherapy: radiotherapy is less strongly recommended in this clinical subset.

Patients who achieve a complete remission should be followed every three months for two years, every six months for a further three years and then annually for at least another five years (grade D).

Patients with refractory or relapsed disease should undergo rescue programs including intensive, non-cross-resistant debulking treatment followed, in chemosensitive patients, by high-dose chemotherapy and autologous SCT (grade B).

As for nodal DLBCL, patients with a high risk of failure with high-dose chemotherapy and autologous SCT, such as progressive disease or chemoresistant relapse, may benefit from experimental approaches including allogeneic SCT (grade C).

Discussion

The existing scientific literature on the management of pulmonary and mediastinal primary non-Hodgkin's lymphomas does not allow evidence-based recommendations to be produced. A systematic literature revision resulted in no comparative randomized intervention studies dealing directly with lung or mediastinal lymphoma. As a consequence, consensus was a critical part of the production of the present guidelines. Experts in the field judged the existing evidence and formulated recommendations in a decision process grounded on the concept that the relative benefit-to-risk balance of the decisions should result from a partially subjective process. The theoretical value of the experts' consensus approach to influencing practice is the assumption that such knowledgeable experts have an implicit and comprehensive mastery of the scientific and practical information that would yield the most appropriate recommendations.

In a preliminary prioritization process, the expert panel listed the most relevant clinical key-questions in the therapeutical pathway of extranodal lymphomas. This was aimed at supporting a rational use of novel technologies still under evaluation, such as PET in the staging process of the lung and mediastinal lymphoma, third generation chemotherapies, and the new therapeutic approaches that are under experimentation, such as rituximab. The resulting recommendations may not receive a comparative evaluation with others resulting from a similar structured group discussion process. In fact, due to the rarity of the pathological condition and the absence of a high grade of scientific evidence, no other published guidelines on extranodal lymphomas were found.

Authorship and Disclosures

PLZ, NP, VP, UV, PG, TC, AJF, MM, and ST participated in the discussion meeetings and in the production of recommendations. GB and ST coordinated the project of guideline production. MM and GB provided the literature revision. GB, MM and PLZ wrote the manuscript. GB received honoraria from Shire. UV received lecture fees by Roche and Bayer. TC received consultation fees from Roche. Mundipharma SpA provided the financial support for literature search, consensus conferences and secretarial personnel for this project. No other potential conflict of interest relevant to this paper was reported.

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