



Management of nodal indolent (non marginal-zone) non-Hodgkin's lymphomas: practice guidelines from the Italian Society of Hematology, Italian Society of Experimental Hematology and Italian Group for Bone Marrow Transplantation

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The Italian Society of Hematology (SIE) and the two affiliated societies (SIES and GITMO) commissioned a project to develop clinical practice guidelines for the treatment of nodal indolent non-Hodgkin's lymphomas (NHL). Key questions clinically relevant to the management of patients with nodal indolent NHL were formulated by an Advisory Committee and approved by an Expert Panel composed of eight senior hematologists. After a comprehensive, systematic review of the literature, the Expert Panel formulated therapy recommendations and graded them according to the supporting evidence. An explicit approach to consensus methodologies was used for evidence interpretation and for providing recommendations based on poor evidence. The Expert Panel formulated recommendations on when to start a lymphoma-specific therapy, which first-line therapy to choose and which therapy to adopt for patients with relapsed, refractory and transformed disease. Treatment deferral was recommended for patients with stage III-IV disease without systemic symptoms, high tumor burden, extranodal disease, cytopenia due to marrow involvement, leukemic phase, serous effusion and high lactate dehydrogenase levels. Patients with stage I-II disease and a low tumor burden should receive frontline external involved-field radiotherapy, while patients with a high tumor burden or a severe prognostic score should receive front-line chemotherapy plus involved-field radiotherapy. Younger patients with stage III-IV disease should receive front-line therapy with anthracycline- or fludarabine-based regimens combined with rituximab, while older patients who are candidates for treatment should receive single-agent alkylating therapy. By using a systematic literature review and an explicit approach to consensus among experts, recommendations for the key therapeutic decisions in patients with nodal indolent NHL are provided.

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

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Non-Hodgkin's lymphomas (NHL) account for 4% of all cancers:¹ of these, about 40% are indolent NHL, which are characterized by a long disease course.^{2,3} The median survival of 8-9 years^{4,5} has improved slightly in the last 20 years,^{6,7} but lymphoma continues to be the principal cause of death in these patients. New strategies have recently been introduced into the therapy of indolent NHL and the integration of older and more recent research results may lead to conflicting conclusions resulting in large variation in clinical practice.

In order to offer the best available treatments to patients, since 2001 the Italian Society of Hematology (SIE) has been supporting the development of clinical practice guidelines in the therapy of selected hematologic diseases. In 2002, the Italian Society of Experimental Hematology (SIES) and the Italian Group for Bone Marrow Transplantation (GITMO) shared this aim with SIE and chose to focus their efforts on the therapy of nodal indolent NHL. Here we present the guidelines pro-

duced during this project. The guidelines are intended to support the clinical practice of hematologists, oncologists and internists who care for patients with lymphoma.

Methods

Organization

The Italian Society of Hematology charged two chairmen (ST and GB) with the development of the present guidelines. They invited an Expert Panel of eight senior hematologists, selected for their expertise in research and clinical practice of NHL. An Advisory Committee was given the duty to perform the systematic review of literature and to guide the consensus phases of developing the guidelines.

Literature search

The Advisory Committee searched the following evidence bases: PubMed, CancerLit, Cochrane Library, EMBASE. The basic searching strategy adopted was:

*Lymphoma/therapy** in MESH. The major hematology, oncology and general medicine journals (Blood, Journal of Clinical Oncology, British Journal of Haematology, Bone Marrow Transplantation, Haematologica, New England Journal of Medicine, Lancet) were manually searched for relevant papers published from 1992 to 2005. Additionally, the proceedings of the latest annual meetings were searched for relevant unpublished evidence: American Society of Hematology (1998-2004), Italian Society of Hematology (2001, 2003), European Haematology Association (2002-2004), American Society of Clinical Oncology (2000-2004). The inquiry was updated to March 1st, 2005. The full reference list (including the abstracts of full papers) is available on request from marchettim@smatteo.pv.it.

Evidence analysis

During the first meeting between the Advisory Committee and the Expert Panel were identified the key therapeutic questions for development of guidelines. The Advisory Committee members performed a systematic literature review by selecting the relevant pieces of evidence and grading their quality. The grading system chosen for the present guidelines is the one produced by the Scottish Intercollegiate Guideline Network (SIGN):⁸ this system primarily classifies evidence according to the study design, thus assigns randomized trials to level 1, cohort and case-control studies to level 2, and case reports to level 3. Studies belonging to level 1 and 2 are further classified into three levels, namely ++, + and -, according to the study and reporting quality. We modified the original classification so as to account for phase II studies, which were assigned level 2, as for cohort studies. Relevant studies (i.e. randomized clinical trials) reported in abstract form only could not be assigned a quality level, but were uniquely classified according to their study design.

Formulation of recommendations

Each member of the Expert Panel formulated recommendations pertinent to a specific key question. For any statement the expert qualified the strength of evidence supporting the recommendation. When no evidence at all was available, the expert suggested expertise-based recommendations.

In order to reach the final set of recommendations, an explicit approach to consensus methods was devised. A first round of consensus on the recommendations proposed by any individual expert was obtained through paper questionnaires, according to the Delphi Panel technique.⁹ The Expert Panel expressed the degree of agreement on any individual recommendation with comments. The final round of consensus was organized through the nominal group

technique¹⁰ along three consensus conferences. Participants at the consensus conferences were individually asked to rate each recommendation, the interpreted strength of evidence and the link between the recommendation and the supporting evidence as appropriate or not appropriate. If an 80% consensus was not achieved, the recommendation was discussed in round-robin fashion and a second vote taken. If an 80% consensus was still not attained, the problem was declared unresolvable and was not considered further.

All the recommendations were graded class A if supported by consistent and applicable level 1 evidence (at least one level 1++ trial or some consistent level 1+ trials), class B if evidence was derived from consistent results of level 2++ studies or was extrapolated from level 1+/1++ trials, class C if supported by grade 2+ studies that could be applied directly to the object population and provided consistent results, or level 1++ studies from different populations (translated evidence), and grade D when supported by poor quality evidence or evidence extrapolated from grade 2+ studies, and thus sustained mainly by the experts' opinion.

Draft guidelines were reviewed by an external panel of expert radiotherapists and by the presidents of the three scientific societies, i.e. SIE, SIES and GITMO.

The present guidelines are intended to be updated in 2007.

Definitions

The Expert Panel agreed on the following definitions to be used in the present guidelines:

Indolent NHL: including follicular lymphoma grade 1-2 and small-cell lymphocytic lymphoma in the absence of criteria for a diagnosis of chronic lymphocytic leukemia (defined according to the modified NCI criteria).¹¹ Immunocytoma, Waldenström's disease and nodal/splenic marginal zone lymphoma were excluded from the present guidelines.

Stage: the Ann Arbor staging system was considered.¹²

High tumor burden: tumor burden was defined by the presence of at least one of the following features:¹³ nodal/extranodal tumor mass > 7 cm, ≥3 nodal sites, each with a nodal diameter >3 cm; any B symptoms; splenic enlargement with inferior margin below the line of the umbilicus; serous effusion; compression syndrome (ureteral, orbital, gastrointestinal); leukemic phase (> 5×10⁹/L circulating lymphoma cells).

Transformed lymphoma: histologic transformation was interpreted as the onset of any area of diffuse large B-cell lymphoma in a follicular lymphoma.¹⁴

Elderly patients: patients aged 65 years or older were

considered elderly. However, the Expert Panel recommended that performance status and comorbidities should also be taken into account in treatment decisions.

Response criteria. Definitions of clinical response are reported in Table 1.¹⁵ It should be noted that most of the reported evidence did not adhere to these recent response criteria.

Complete molecular response: sustained polymerase chain reaction negativity.

Risk scoring systems: The International Prognostic Index (IPI),¹⁶ the Italian Lymphoma Intergroup (ILI),⁵ and the Follicular International Prognostic Index (FLIPI)¹⁷ risk scoring systems were adopted to stratify patients, when appropriate.

Results

Indications to start treatment

The indication to start treatment in patients with nodal indolent NHL was evaluated by three trials that randomized patients with *de novo*, asymptomatic, advanced-stage and low tumor burden indolent NHL to either chemotherapy or a strategy of watchful waiting.¹⁸⁻²⁰ Two level 1- old trials compared watchful waiting with ProMace-MOPP polychemotherapy,¹⁸ prednimustine or interferon¹⁹ in stage II-IV patients

and did not show any significant difference in 4- and 5-year survival, respectively, except for a significant prolongation of failure-free survival with polychemotherapy.¹⁸ A more recent randomized trial (level 1+)²⁰ with a 16-year median follow-up, reported that median overall survival was 5.9 years for patients treated with oral chlorambucil versus 6.7 years ($p=0.84$) for those whose management was limited to observation. Cause-specific survival was also similar in the two arms: 9 vs 9.1 years, respectively. The median time to first systemic treatment was 2.7 years in the group randomized to watchful waiting. At multivariate analysis, age younger than 60 years, erythrocyte sedimentation rate 20 mm/h or less, and stage III disease conferred a significant advantage in both overall survival ($p<0.0001$, 0.03, and 0.03, respectively) and cause-specific survival ($p=0.002$, 0.008, and 0.001, respectively).²⁰

A strategy of watchful waiting for patients with localized stage disease was evaluated by only two level 2 studies.^{21,22} The first one reported the outcome of 26 patients with stage I indolent NHL followed without any therapy after removal of all evident disease by diagnostic biopsy.²¹ The overall survival rate of the population at 5 and 7 years was 82.5% and 69%, respectively, and 50% of the patients were relapse-free after a median follow-up of 4.6 years. In a second retrospective study, 43 patients with

Table 1. Response criteria for lymphoma (adapted from: Cheson, *J Clin Oncol* 1999).¹⁵

Response Category	Lymph Nodes	Other sites	Bone Marrow
Complete Response (CR)	Regression to ≤ 1.5 cm GTD in nodes >1.5 cm before therapy and to ≤ 1 cm GTD (or by more than 75% SPD) in nodes 1.1-1.5 cm before therapy	Regression or maintenance of normal size	Normal
Complete Response undefined (CRu)	Possible residual nodes >1.5 cm GTD but with a SPD regression of $>75\%$	Regression or maintenance of normal size	Normal or indeterminate (increased number or size of aggregates without cytological or architectural atypia)
Partial Response (PR)	$\leq 50\%$ decrease in SPD of the 6 largest nodes or nodal masses and no increase in size of other nodes	Spleen and liver: no increase in size; regression by $>50\%$ in nodules No new sites of disease.	Irrelevant
Relapse (for patients with CR or CRu at the end of therapy)	Appearance of any new nodes and/or increase by $\geq 50\%$ in the size of previously involved nodes	Appearance of any new lesion and/or increase by $\geq 50\%$ in the size of previously involved sites	Appearance or reappearance of involvement
Progression (for patients on therapy or with PR or non-responders at the end of therapy)	$\geq 50\%$ increase from nadir in SPD of any previously abnormal node	Appearance of any new lesion	Appearance or reappearance of involvement

GTD: greatest transverse diameter; SPD: sum of the products of the greatest diameter.

untreated stage I and II follicular lymphoma deferred initial therapy for various reasons.²² Only 16 (37%) patients received any treatment within 7 years from the diagnosis. The estimated 10-year overall survival rate was 85% after a median follow-up of 86 months.

After a review of 21 observational studies documenting that median overall survival exceeded 10 years,²³⁻⁴² the Expert Panel judged that the evidence provided from these studies recommends that a strategy of watchful waiting is appropriate only in patients with advanced disease. These results were especially valuable in elderly patients, in whom quality of life and non-lymphoma-related causes of death are more relevant. The same conclusion cannot be completely supported for younger patients, since the existing evidence in favor of this strategy does not account for novel therapies and the chance of needing chemotherapy is high in a short time frame. The only possible exceptions are patients with limited disease without residual lymphoma after excisional biopsy, who attain a very good outcome despite no further treatment.

Recommendations

Treatment can be safely deferred without disadvantage to survival for patients with stage III-IV disease, provided that none of the following features occurs: systemic symptoms, high tumor burden, extranodal disease, cytopenia due to marrow involvement, spleen involvement, leukemic phase, serous effusion, erythrocyte sedimentation rate > 20 mm/h, high lactate dehydrogenase levels [grade A]. A policy of watchful waiting is particularly advisable in elderly patients (> 70 years) with the above characteristics [grade B].

Patients with stage I-II disease should not be managed with a frontline strategy of watchful waiting; however elderly patients with stage I disease and no symptoms whose lactate dehydrogenase level is not elevated may be safely observed without treatment, provided that there is no residual disease after excisional biopsy [grade D].

First-line therapy

Localized stage I-II

The Advisory Committee selected for review 14 papers addressing radiation therapy as the sole treatment for this group of patients. The definitions used in literature for the radiation fields vary considerably. *Involved field* radiotherapy is most commonly used in localized lymphomas and implies treatment to the nodal region or extranodal sites and, if involved, its immediate lymph node drainage area. A treatment plan including the adjacent, second echelon not involved lymph nodes is usually considered *extended field* radiotherapy, even if true extended field therapy should refer to the classical Hodgkin's fields.

Evidence on radiotherapy in localized stage I-II disease was derived mostly from poor quality phase II

studies or case series.²³⁻³⁶ Patients with stage I and II follicular lymphoma treated with a radiation dose of 30 to 36 Gy delivered in 15 to 20 fractions over 2-4 weeks experienced local control rates of more than 95%. Moreover, radiation therapy alone achieved excellent survival and long-term disease control: in a recent update of the Princess Margareth Hospital experience,²³ overall survival rates at 5 and 10 years were 79% and 62%, while disease-free survival rates were 56% and 41%, respectively. Several retrospective papers showed similar clinical outcomes, with 5-year overall survival rates ranging from 70% to 90%.²⁴⁻³⁶ There is insufficient information to assess the impact of doses lower than 30 Gy on local control in unselected cohorts of patients with follicular lymphoma. Six randomized level I-II trials³⁷⁻⁴² reported that the addition of chemotherapy to first-line radiotherapy does not prolong survival in patients with stage-I-II NHL; however, only one trial, employing chlorambucil, selectively enrolled and analyzed low-grade NHL patients.⁴² Phase II studies from the MD Anderson Center⁴³⁻⁴⁶ reported a very high failure-free survival, i.e. 76% at 10 years, with COP/CHOP-like chemotherapy added to involved field radiotherapy, which was about 20-25% higher than the rate achieved with involved field radiotherapy alone.

Within the subset of patients with limited stage I-II disease, high tumor burden and high risk (IPI>1 or ILI >2) were considered negative predictors of progression-free survival in three phase II studies.^{34,36,46} Moreover, the Expert Panel judged that long-term toxicity should be a relevant criterion for choosing either involved field or extended field radiotherapy and that the involved field approach should therefore be considered a standard in the setting of stage I-II follicular lymphoma. The Expert Panel deemed the strength of evidence sufficient to recommend frontline chemotherapy followed by involved field radiotherapy only in stage I-II patients with a high tumor burden.

An innovative approach to the treatment of localized stage disease with low tumor burden might be the association of immunotherapy (rituximab) with radiotherapy. So far, no studies have been reported which compare radiotherapy alone to the combination of radiotherapy and rituximab.

Advanced stage III-IV

Extended field radiotherapy alone has been evaluated in stage III follicular lymphoma in three retrospective phase II studies (grade 2).⁴⁷⁻⁴⁹ The median overall survival was about 10 years. In the Stanford study,⁴⁹ the subset of patients with *limited* stage III disease (defined as fewer than 5 disease sites, tumor masses less than 10 cm and no B symptoms), showed a better outcome, i.e. a failure-free survival rate of 88% at

over 23 years follow-up. Two randomized studies (grade 1)^{50,51} compared chemotherapy alone with a combined approach (chemotherapy plus extended field radiotherapy), or central lymphatic irradiation alone versus chemotherapy alone. In the first study (grade 2+),⁵⁰ the long term follow-up showed that the combined approach achieved significantly better disease control, but not significantly longer overall survival or failure-free survival. In the second (grade 2-),⁵¹ the two arms showed similar overall survivals and relapse-free survivals, but a significantly higher rate of molecular remissions was achieved by chemotherapy.⁵¹ The rate of second malignancies reported in the first study was low in both the treatment arms,⁵⁰ while a significantly higher rate of secondary cancers was reported in patients receiving central lymphatic irradiation.⁵¹

Because of the high risk of secondary cancers with extended radiotherapy/central lymphatic irradiation, as compared with chemotherapy alone, the Expert Panel judged radiotherapy not to be a valuable first-line therapy in patients with advanced disease. However, extended-field radiotherapy alone could be of benefit to selected patients with *limited* stage III disease, provided that they prefer to avoid chemotherapy or when an absolute contraindication to chemotherapy exists.

The Advisory Committee analyzed 37 randomized trials comparing different regimens of chemotherapy in advanced stage indolent lymphomas. Seven studies compared alkylating agents, 12 anthracycline-based chemotherapies, 4 purine analogs and 14 CVP-like regimens. Single agent chemotherapy with chlorambucil or cyclophosphamide was widely used in advanced stage indolent lymphomas. Both drugs are able to induce an overall response rate ranging from 54-72% with a complete response rate from 30 to 70% and a median overall survival ranging from 4.5 to 9 years.⁵²⁻⁵⁵

Single agent chemotherapy was compared to polychemotherapy with or without an anthracycline: although some studies reported a higher response rate with polychemotherapy, neither cyclophosphamide-containing regimens, such as CVP,⁵⁶⁻⁵⁸ nor anthracycline-containing regimens⁵⁹⁻⁶¹ were able to produce a better outcome than that afforded by single agent chemotherapy. These data were confirmed in a systematic review of 8699 patients.⁶² Although chlorambucil toxicity is limited, long-term exposure to cumulative alkylating doses may induce impairment of peripheral blood stem cell mobilization and a higher risk of secondary myelodysplasia.^{63,64} On the basis of the evidence on adverse events, the Expert Panel judged that single agent chemotherapy should be avoided in young patients.

Adriamycin was introduced in the 1980s within

polychemotherapy regimens such as CHOP: since then, five prospective and one retrospective study have reported outcomes of first-line therapy with CHOP in a total of 1,343 patients.⁶⁵⁻⁷¹ Consistent data are lacking on superior outcomes with CHOP as compared with CHOP-like regimens or with CVP-like regimens.^{72,74}

Good outcomes have been reported for other anthracycline-based regimens: in the SWOG 8809 trial,⁷⁵ ProMACE-MOPP achieved some kind of response in 83% of the patients and COPA in 86%.⁷⁶ However, the addition of epirubicin to chlorambucil did not improve either the response rate or survival in non-follicular indolent NHL, as reported by a recent randomized trial by the Italian Lymphoma Intergroup.⁵⁹

In the nineties, purine analogs became available for clinical research.⁷⁷ Single-agent therapy with fludarabine showed efficacy in indolent lymphoma with an overall response rate of 60-70% and a complete response rate of 30-37%.^{78,79} In an EORTC randomized trial, fludarabine produced significantly better overall and complete response rates than did CVP; however, neither time to progression nor overall survival differed between the two arms.⁸⁰ Fludarabine-containing regimens with anthracyclines (mitoxantrone ± dexamethasone or idarubicin)⁸¹⁻⁸⁵ or cyclophosphamide⁸⁶⁻⁸⁸ were able to induce a high overall response rate (from 81% to 94%) with complete response rates ranging from 39% to 79% and a 4-year progression-free survival from 38% to 90%. Moreover, fludarabine used in combination with mitoxantrone (FM), or with mitoxantrone and dexamethasone (FND) induced bcl2 rearrangement negativity in 21% to 56% of patients.^{82,85,86} A comparison across phase II studies suggested that fludarabine used in combination was more effective than fludarabine alone, however the only randomized trial comparing single-agent fludarabine with fludarabine in combination with idarubicin yielded comparable response rates, although the progression-free survival rate was better in the combination arm.⁸¹ The effectiveness of FM or FND was compared to that of CHOP-like regimens in three recent randomized trials.^{86, 89, 90} In an Italian randomized trial,⁸⁶ frontline FM provided higher complete response and molecular response rates than did the CHOP chemotherapy regimen. However, no survival data are currently available in support of a better outcome with FM.

Although fludarabine is a well tolerated agent, adverse effects include the risk of opportunistic infection, mainly *Pneumocystis carinii*, and impairment of peripheral blood cell mobilization. Evidence on the optimal strategy for infection prophylaxis was derived only from retrospective studies (grade 2).^{91,92} These studies documented that lack of *Pneumocystis*

carinii prophylaxis was the only significant variable that differentiated patients who developed opportunistic lung infections from those who did not, and that corticosteroid treatment was associated with an increased risk of opportunistic infections. After discussion, the Expert Panel agreed on the wisdom of prophylactic treatment with trimethoprim sulphamethoxazole, at least in patients receiving fludarabine and concomitant steroids. Impaired stem cell mobilization after fludarabine-containing regimens was reported by a few studies,⁹³⁻⁹⁵ and these results did not concord with those of other studies.⁸⁹

One randomized trial (level 1-) showed that front-line single-agent interferon did not significantly improve progression-free or overall survival, compared to a strategy of watchful waiting or single agent chemotherapy.¹⁹ Several randomized trials proved that the association of interferon with mono-chemotherapy or polychemotherapy not containing doxorubicin did not improve overall or complete response rate and was more toxic.⁹⁶⁻⁹⁸ Interferon combined with doxorubicin-based chemotherapy (CHVP or COPA) was reported to increase progression-free survival;^{76,99} however, overall survival was significantly prolonged in only one trial.¹³ Combining interferon with CHVP polychemotherapy significantly improved response rate, failure-free survival and overall survival in comparison to fludarabine as a single-agent.⁷⁹ However, 39% of the patients allocated to interferon combination therapy dropped out because of severe fatigue or toxicity. In a meta-analysis of eight randomized trials, significant improvements in 5-year overall survival and progression-free survival were reported (level 1-),¹⁰⁰ but a further meta-analysis reported that the benefit of interferon was more evident in patients responding to combined interferon and anthracycline-based polychemotherapy.¹⁰¹ In a subsequent meta-analysis based on individual patient data from ten randomized trials,¹⁰² adding interferon to the initial chemotherapy did not significantly improve the response rate; however, interferon significantly improve overall survival when associated with a dose higher than 5 million units and a cumulative dose over 36 million units (*relatively intensive* chemotherapy). The Expert Panel judged that the toxicity of interferon when included in first-line chemotherapy did not balance the possible survival benefit. This conclusion was also grounded on quality-adjusted survival analysis and cost-effectiveness analysis exploited in two studies.^{103,104}

Rituximab was used as a single agent in untreated patients with stage III-IV indolent NHL.¹⁰⁵⁻¹⁰⁸ Overall response rates ranged from 72% to 100% and a molecular response in peripheral blood was achieved by 53%. At one year, 69% to 80% of patients were free of progression, and at 3 years from 32% to 49%

were progression-free. After a median follow-up of 32 months, neither disease-free survival nor overall survival resulted significantly longer in patients randomized to rituximab than in those assigned to CNOP or CHOP plus rituximab.¹⁰⁸ No controlled study has compared a strategy of watchful waiting or radiotherapy with rituximab monotherapy in this subset of patients.

First-line association, either concurrent or sequential, of rituximab with chemotherapy was explored in candidates for treatment. Two randomized studies recently provided evidence on the efficacy of rituximab combined with CHOP or CVP regimens in advanced-stage follicular lymphoma.^{109,110} The addition of rituximab to first line chemotherapy (CVP or CHOP) significantly increased overall and complete response rates and prolonged time to treatment failure. In both studies, the follow-up was shorter than 3 years and no data on overall survival have been provided. In addition, two other randomized trials published in abstract form,^{111,112} confirmed the advantage of combining rituximab with chemotherapy regimens (CHVP+interferon and MCP respectively). Moreover, two recent phase II studies reported a prolonged clinical and molecular remissions in newly diagnosed patients with indolent NHL treated with CHOP chemotherapy combined with rituximab,¹¹³ and high clinical and molecular response rates to rituximab in combination with fludarabine chemotherapy.^{68,114} Although the chemotherapy regimens varied among the studies, based on the evidence available on the efficacy of adding rituximab to chemotherapy, the Expert Panel judged it appropriate to combine rituximab with conventional chemotherapy regimens in first line treatment.

The optimal association of rituximab with chemotherapy is still a matter of debate. The only evidence was provided by a recent randomized study in which concurrent administration provided better progression-free survival than did sequential administration.¹¹⁵ However, the Expert Panel judged this evidence not sufficient to give recommendations.

A phase II trial (grade 2++) reported the results of radio-immunotherapy with iodine I¹³¹ tositumomab regimens as single initial treatment in 77 previously untreated patients with follicular lymphoma.¹¹⁶ The overall response was 95% (complete remission 75%) with a molecular response rate of 80%. After a median follow up of 5.1 years, 59% were alive without progression and hematologic toxicity was moderate. Moreover, three phase II trials reported the results of combination chemo-radio immunotherapy (iodine I¹³¹ tositumomab) regimens in previously untreated follicular lymphoma patients, suggesting that this combination could be a highly effective and well tolerated regimen for initial therapy of patients with follicular

lymphoma.¹¹⁷⁻¹¹⁹ However, a comparison of long-term outcomes with standard chemotherapy or with radio-immunotherapy is not possible, yet. Therefore, the Expert Panel deemed radio-immunotherapy appropriate only in well-designed clinical trials.

Randomized phase III studies assessing frontline autologous stem cell transplantation (SCT) were recently reported by the GELA, GOLEAMS and GLSG study group.¹²⁰⁻¹²² The GELF94 trial reported a 12% better 7-year overall survival in 192 untreated patients with follicular lymphoma and a high tumor burden who received frontline CHOP and autologous SCT (with total body irradiation conditioning), as compared with 209 patients randomized to CHVP and interferon.¹²⁰ The GOLEAMS 064 trial, however, did not report a significant advantage in overall survival of autologous SCT at a median 56 months of follow-up, while 5-year event-free survival increased from 37% to 59%.¹²¹ The randomized trial of the German Low-grade Study Group (GLSG) showed that consolidation with myeloablative radiochemotherapy followed by autologous SCT, after CHOP-like therapy, compared to conventional interferon maintenance, prolonged progression-free survival in 307 patients with follicular lymphoma in first remission.¹²²

None of these three randomized studies did a comparison of frontline autologous SCT with frontline chemoimmunotherapy. Considering that no plateau was evident in survival curves after autologous SCT and that evidence on the role of chemoimmunotherapy is rapidly growing, the Expert Panel considered that first-line autologous SCT should be reserved to patients enrolled into prospective clinical trials.

Molecular restaging

Several prospective (level 2+) studies documented that the achievement of a sustained molecular response after conventional chemotherapy with or without rituximab was a favorable prognostic factor and correlated with prolonged failure-free survival.^{113,114,116,123} Despite some conflicting results being reported,¹²⁴ the Expert Panel judged that it is appropriate to assess molecular remission in patients who achieve complete remission after frontline chemotherapy.

Recommendations

Before deciding the therapy for patients with indolent NHL, lymphoid tissue should be tested for CD20 antigen expression [grade D].

Patients with stage I-II disease and low-tumor burden should receive external involved field radiotherapy only [grade B], at the dose of 30-36 Gy. Adjuvant chemotherapy is not recommended in these patients [grade D].

Patients with stage I-II disease and a high tumor burden

or an IPI score >1 or ILI score >2 or FLIPI >2 should receive frontline chemotherapy plus radiotherapy [grade D].

Patients with stage III-IV disease and not candidates for a watch and wait strategy, should be treated with frontline chemotherapy [grade B].

Radiotherapy alone is not recommended for patients with advanced stage disease [grade B], however, patients with stage III disease and a low tumor burden may be treated with external radiotherapy alone if they prefer to avoid chemotherapy or if there is a contraindication to chemotherapy. The long-term toxicity of radiotherapy should be discussed with the patient and the patient should be carefully monitored [grade D].

Frontline chemotherapy, either single-agent alkylators, anthracycline-based polychemotherapy or fludarabine-based polychemotherapy, should be chosen according to the characteristics of the patient and the disease [grade B].

Rituximab, either concurrent or sequential, should be added to frontline conventional chemotherapy [grade A]. Younger patients should not receive single-agent alkylating chemotherapy because it is not able to induce molecular remission and it reduces stem cell mobilization potential [grade C].

Interferon is not recommended as induction therapy, either alone [grade A] or in association with chemotherapy [grade A].

Molecular response should be checked at the end of first-line therapy in all patients with an informative probe who reach a complete clinical remission [grade D].

Maintenance therapy

Seven trials randomized a total of 1250 patients to either interferon maintenance therapy or observation only.^{75,96-98,125-129} The drug (3-5 MU three times weekly) was administered for 1 or 2 years or until progression. A statistically significant increase of progression-free survival was found in a few studies,^{98,126,127} while only one study¹²⁶ was able to demonstrate an increase in overall survival. Two meta-analyses^{100,101} pooled the data of randomized trials employing interferon but did not separately calculate the outcomes of maintenance therapy, therefore the results cannot be applied to the specific effect of interferon maintenance. A recent meta-analysis¹⁰² deeply analyzed ten randomized trials and concluded that interferon could not improve overall survival when administered as a maintenance therapy. Moreover, long-term interferon therapy severely impairs patients' quality of life and such a detrimental effect may offset the potential clinical benefit.¹⁰³ The Expert Panel agreed not to recommend universal interferon maintenance therapy in this clinical setting.

Preliminary results supported the positive role of maintenance rituximab infusion on response duration in patients with follicular lymphoma.¹³⁰ Two randomized studies have been reported so far confirming

these results.^{114,131} Recently, a Swiss trial¹³² showed that prolonging rituximab monotherapy from 3 to 11 months induced a relevant prolongation of event-free survival in 185 patients with follicular lymphoma, 67% of whom were chemotherapy-naïve. Another randomized trial of 322 patients, only partially reported at scientific meetings, was prematurely interrupted because maintenance rituximab significantly prolonged progression-free survival after CVP with a 4-year progression-free survival of 58% in the maintenance arm versus 34% in the no-maintenance arm.¹³³ Two phase II studies^{134,135} employed rituximab in association with interferon; however they did not allow comparison with rituximab as single-agent therapy. Rituximab was explored in patients with minimal residual disease after autologous SCT:^{136,137} it proved to be able to induce molecular response in more than half of the patients and this response lasted more than 6 months. The Expert Panel judged that the real long-term clinical benefits of rituximab in this setting deserve more comparative studies with adequate follow-up.

Maintenance chemotherapy was assessed before 1990 by two randomized studies, showing that intermittent chlorambucil or BCVP provided a significant improvement in progression-free survival,^{138,139} without advantage for overall survival. The Expert Panel judged that myelotoxic therapies should be spared in patients who may subsequently be candidates for effective salvage therapies including chemo-immunotherapy or high-dose therapy with autologous SCT.

Recommendations

Chemotherapy or interferon is not recommended as maintenance therapy in low grade NHL [grade A]. The use of rituximab in the maintenance strategy should be considered investigational.

Therapy for patients who do not achieve a complete response to frontline therapy

Patients with a partial response

The Expert Panel found it difficult to pronounce on the treatment of patients not achieving a complete response after first-line therapy because very few studies have specifically addressed this issue. Many studies enrolled a mixed cohort of patients with either partial response or no response hampering the interpretation of the results.¹⁴⁰⁻¹⁴² In principle, the delivery of an alternative course of chemotherapy in patients with a partial response, may allow further tumor reduction along with the possibility of achieving a complete response. The sequential addition of rituximab in patients achieving a partial response after first-line anthracycline- or fludarabine-based chemotherapy, was reported to increase overall

response rates to over 90% and complete response rates from 50% to 80% in phase II studies.^{86,143-145} Therefore, the Expert Panel deemed rituximab a possible consolidation option for patients with indolent NHL. However, even in the absence of strong evidence, the Expert Panel agreed that an exception to this indication was the case of non-follicular lymphoma with a high number of circulating CD20⁺ cells, i.e. small lymphocytic lymphoma.

Indirect evidence supported the application of frontline autologous SCT in those patients who did not achieve complete remission after first-line therapy. The use of autologous SCT as a consolidation treatment has been recently evaluated in a randomized trial: the study compares SCT to interferon in patients with follicular lymphoma achieving a complete or partial response after CHOP chemotherapy.¹²² The results of this trial showed that autologous SCT significantly prolonged 5-year progression-free survival both in the whole study population (64.7% vs 33.3%) and in the subset with an initial partial response (63% vs 32%). However, an increased risk of secondary neoplasms has been observed that might counter-balance the benefit of autologous SCT.^{121,146} Thus, the Expert Panel judged that this approach was to be reserved only to patients with negative prognostic factors.

Finally, radioimmunoconjugates have been considered a consolidation option for patients with follicular lymphoma who have achieved a partial response after chemotherapy: a phase II study (grade 2) in this setting showed an increased rate of complete response without a relevant increase of toxicity.¹⁴⁷

Non-responding patients

Evidence from phase II studies (grade 2) supports the conclusion that patients who do not respond to single-agent alkylators as first-line therapy might benefit from an anthracycline- or fludarabine-based chemotherapy.^{84,141-143} However, stronger evidence supports the use of rituximab, as reported by 13 phase II studies and a randomized trial.¹⁴⁸ In refractory/relapsed patients, rituximab monotherapy produced overall response rates of 21% to 63%, and less than 24% complete responses. Molecular response was achieved in over 50% of bcl2⁺ patients, however molecular response did not correlate with complete responses.¹⁴⁹ Association of rituximab with chemotherapy is much more effective than single-agent therapy.¹⁵⁰ In phase II studies enrolling patients with relapsed/ resistant follicular lymphoma, the association of CHOP-like or fludarabine-based polychemotherapy with rituximab gave overall responses rates ranging from 82% to 97%. Moreover, chemoimmunotherapy with rituximab achieved molecular response in 80-90% of bcl2⁺ patients. The elderly did

not achieve lower response rates than the younger. Two recent randomized trials in patients with relapsed and refractory FL reported a prolonged progression-free survival with the addition of rituximab to fludarabine, cyclophosphamide and mitoxantrone (FCM)¹⁵¹ or MCP chemotherapy.¹⁵²

A further therapeutic option in non-responding patients is autologous SCT. Evidence on the use of autologous SCT in primary refractory patients has been derived from mixed cohorts also including relapsed patients. The available studies provided evidence that delaying high-dose therapy and SCT impaired mobilization potential,^{63,64,153-157} and that the outcomes after autologous SCT were heavily impaired in chemorefractory patients.¹⁵⁸⁻¹⁶⁴

A high number of trials indicate that young patients with a sibling donor should be candidates for allogeneic SCT as soon as they show non-response to standard chemotherapy.¹⁶⁵⁻¹⁷³ The incidence of post-transplant secondary myelodysplastic syndromes or acute myeloid leukemia (sMDS/AML) is very low;^{174,175} however, allogeneic SCT is associated with an overall transplant-related mortality of about 20% according to the latest reports^{175,176} and transplant-related mortality was higher in chemorefractory patients.¹⁷⁷ Long-term molecular remissions are frequent, and a survival plateau in patients alive at 2 years from transplant was reported.¹⁷²⁻¹⁸⁰ Positive predictors of overall survival were mainly the negative predictors of transplant-related mortality, which had the major impact on survival. As a matter of fact, age lower than 40 years, a good performance status and chemosensitivity all showed hazard ratios of about 0.5 at multivariate analysis.¹⁷⁶ Radio-immunotherapy is also a therapeutic option in patients not responding to first-line chemotherapy. In refractory indolent NHL β -emitting anti-CD20 antibodies, i.e. tositumomab and ibritumomab, administered according to the schedules reported in *Appendix 1*, produced an overall response rate of 60%-70% and complete responses in 20%-35% of patients, as shown by several phase II studies.¹⁸¹⁻¹⁹⁰ Grade IV neutropenia occurred in 5% to 17% of the patients treated with tositumomab,^{182,184} and in 30% to 35% of those receiving ibritumomab;¹⁸⁵ grade IV thrombocytopenia occurred in 3% of the patients after tositumomab¹⁸³ and 7% to 16% after ibritumomab.¹⁸⁷ Serious infections occurred in 5% to 7% of the patients.^{184,190} Nadir platelet and neutrophil counts occurred 7-9 weeks after administration of the radio-immunoconjugate.¹⁹⁰ Similar rates of hematologic complications were observed in younger and older patients.¹⁸⁵ The risk of severe complications increased in patients with bone marrow involvement. Long-term complications of radio-immunoconjugate include sMDS, which occurred in 8.4% of the patients treated with tositumomab.¹⁸² The annual

incidence rate of sMDS was estimated to be 1.4% from a pooled analysis of 7 trials; however, in heavily pretreated patients in a large series, the incidence rate was 3.8% per year and was associated with an additional 2% per year risk of non-hematologic non-skin cancers.^{191,192} Cytogenetic abnormalities in chromosome 5 or 7 were found pre-treatment in nearly all of the patients who subsequently developed sMDS.^{191,192} Limited data are available on the rate of sMDS after ibritumomab therapy: a 1.5% rate was evident at a follow-up shorter than 2 years.¹⁸⁵ Patients treated with tositumomab must have their thyroid stimulating hormone values monitored and receive thyroid protection since elevated levels occur in 8.5% of the patients, despite thyroid protection.¹⁸⁴

No clinical trial specifically addressed patients who achieved a partial response after frontline radiotherapy nor patients progressing during watchful waiting: the Expert Panel deemed that recommendations for first-line therapy were appropriate for this group of patients, too.

Recommendations

Patients who achieved a partial remission after first-line therapy may be considered for consolidation treatment with one of the following options: rituximab, autologous SCT, radioimmunoconjugates (either tositumomab or ibritumomab) [grade C].

Patients not responding to first-line chemotherapy should receive further treatment provided that they are symptomatic, or have a threatened organ function, or a cytopenia secondary to bone marrow infiltration, or massive bulky disease at presentation, or a steady progression over the last 6 months [grade D].

Patients not responding to first-line alkylating agent-based chemotherapy can be offered an anthracycline- and/or fludarabine-based regimen with rituximab [grade C].

Patients not responding to first-line anthracycline- or fludarabine-based chemotherapy should be offered high dose chemotherapy and SCT (autologous or allogeneic) [grade B]: if SCT is not feasible it is recommended that these patients receive radioimmunoconjugates (either tositumomab or ibritumomab) [grade C].

Therapy for relapsed patients

Histopathological transformation of low-grade follicular lymphoma to large-cell aggressive NHL occurs frequently in the course of follicular lymphoma, especially within the first 6 years from diagnosis.¹⁹³⁻¹⁹⁵ Transformed lymphomas have an aggressive disease course^{193,197,198} and require a specific treatment (*see next section*); therefore, the Expert Panel agreed that histopathological reassessment is mandatory before any treatment decision is made in relapsed patients. Literature review identified 26 reports of patients undergoing autologous SCT after relapse of an indo-

lent NHL. Non-randomized studies provided evidence that transplant-related mortality in patients 60-70 years of age undergoing autologous SCT is similar to that in younger patients, ranging from 0 to 10%.¹⁹⁹⁻²⁰⁴ The major long-term complications of autologous SCT were sMDS, occurring in 3% to 15% of patients within 5 years after transplantation.²⁰⁵⁻²¹¹ The lowest incidence rate of sMDS, derived from the EBMT Working Party, was 3% at 5 years in nearly 5000 lymphoma patients.²¹⁰ However, the incidence reached up to 24% at 10 years and was higher in follicular or indolent lymphoma than in aggressive NHL.^{207,212,213} A randomized comparison provided strong evidence that about 8% of patients with indolent NHL undergoing myeloablative radiochemotherapy followed by SCT could be expected to develop sMDS, as compared with less than 1% of patients receiving conventional therapy.²¹³ The major predictors of sMDS after transplantation are age,^{214,215} cumulative dose of alkylating agents before transplantation,²¹⁵⁻²¹⁷ and abnormal pre-transplant cytogenetics.²¹⁸ The last parameter had a very high negative predictive power, since none of the patients with normal cytogenetics developed sMDS after transplant; however, its positive predictive power ranged from 15% to 85% in the few studies reported, since abnormal cytogenetics interacted with other factors predictive of the development of sMDS.²¹⁸⁻²²¹

Autologous SCT was shown to be superior to standard chemotherapy in six retrospective controlled studies²²²⁻²²⁸ and in a randomized trial.²²⁹ The CUP trial,²²⁹ comparing standard chemotherapy (CHOP) to autologous SCT in relapsed follicular lymphoma, was stopped prematurely because of poor patient accrual: after 2 years of follow-up the trial showed a nearly 50% reduction of relapse rate and statistically significant improvements in progression-free and overall survival by using SCT (hazard ratio for overall survival, 0.43). Moreover, a similar conclusion was reported by a randomized trial enrolling patients with intermediate/high-grade NHL.²³⁰

At multivariate analysis, status of disease at transplant was the best predictor for disease-free survival: the largest cohort of patients with indolent NHL undergoing autologous SCT reported 12-year overall survival and disease-free survival were 61% (95% CI: 53-69%) and 37% (95% CI: 27-47%), respectively, in 419 patients with follicular lymphoma.²¹¹ Therefore, the Expert Panel deemed evidence strong enough to recommend autologous SCT in relapsed patients who achieve a response to re-induction chemotherapy. Only one study specifically reported the outcome of patients with non-follicular indolent NHL after autologous SCT: among 21 patients the overall survival at 6 years was 68%.²³¹ Several other reports did not distinguish between follicular and non-follicular indo-

lent NHL; therefore, the Expert Panel considered it appropriate to translate the recommendations for follicular lymphoma to other non-follicular indolent NHL.

Conditioning with total body irradiation was reported to increase the incidence of sMDS by up to 5-fold.^{215,232} Contrasting data were reported by retrospective studies comparing conditioning regimens based or not on total body irradiation: one study reported a detrimental effect on overall survival,²³³ while the opposite was shown for fractionated total body irradiation in another study,²³⁴ and overall survival was not different in most of the reports.^{214,235-237}

Conditioning strategies for autologous SCT have recently incorporated radio-immunotherapy regimens. A retrospective case-control study of 125 patients with follicular lymphoma reported lower transplant-related mortality and higher overall survival (hazard ratio, 0.3) and progression-free survival (hazard ratio, 0.5) in patients conditioned with tositumomab, with no significant increase in the rate of sMDS.^{238,239} The outcomes were apparently better in patients conditioned with radio-immunoconjugates than with total body irradiation;²⁴⁰ however, prospective controlled studies have not confirmed such a benefit, yet.

Lymphoma cells often contaminate bone marrow and peripheral blood stem cell collections and may contribute to relapse after autologous SCT.²⁰⁴ One randomized and four high-quality retrospective cohort studies reported the outcomes of *in vitro* purging with anti-B-cell monoclonal antibodies.^{175,227,233} The most recent retrospective large cohort confirmed prior reports²⁰⁵ and significant 26% and 32% reductions were observed in 5-year relapse rate and overall survival, respectively, in patients receiving an *in vitro* purged harvest. In contrast, the CUP trial²²⁹ reported similar outcomes after purged and unpurged harvests in 89 patients with follicular lymphoma, but the trial was prematurely stopped after enrolling only 89 patients, so it was underpowered.

More recently, *in vivo* purging was achieved by administering rituximab prior to autologous SCT. Three-year relapse-free survival and 2-year progression-free survival rates were 84% and 97%, respectively, in the most recent studies.^{241,243} Studies reported a lower harvest yield, a longer time to engraftment and later immune reconstitution in patients undergoing autologous SCT after having received rituximab in the 6 preceding months,²⁴³ while others did not detect such detrimental effects.²⁴⁴⁻²⁴⁷ The Expert Panel judged that definitive data on the efficacy of rituximab on purging are not available due to very different schedules and patient selection (often including mantle-cell lymphomas) among the studies and due to the lack of controlled studies.

Table 2. The complete set of recommendations for indolent non-Hodgkin's Lymphomas (NHL).

Treatment can be safely deferred without disadvantage to survival for patients with stage III-IV disease, provided that none of the following features occurs: systemic symptoms, high tumor burden, extranodal disease, cytopenia due to marrow involvement, spleen involvement, leukemic phase, serous effusion, erythrocyte sedimentation rate > 20 mm/h, high lactate dehydrogenase levels [grade A].

A policy of watchful waiting is particularly advisable in elderly patients (> 70 years) with the above characteristics [grade B].

Patients with stage I-II disease should not be managed with a frontline strategy of watchful waiting; however elderly patients with stage I disease and no symptoms whose lactate dehydrogenase level is not elevated may be safely observed without treatment, provided that there is no residual disease after excisional biopsy [grade D].

Before deciding the therapy for patients with indolent NHL, lymphoid tissue should be tested for CD20 antigen expression [grade B].

Patients with stage I-II disease and low-tumor burden should receive external involved field radiotherapy only [grade B], at the dose of 30-36 Gy.

Adjuvant chemotherapy is not recommended in these patients [grade D].

Patients with stage I-II disease and a high tumor burden or an IPI score>1 or ILI score>2 or FLIPI>2 should receive frontline chemotherapy plus radiotherapy [grade D].

Patients with stage III-IV disease and not candidates for a watch and wait strategy, should be treated with frontline chemotherapy [grade B].

Radiotherapy alone is not recommended for patients with advanced stage disease [grade B], however, patients with stage III disease and a low tumor burden may be treated with external radiotherapy alone if they prefer to avoid chemotherapy or if there is a contraindication to chemotherapy. The long-term toxicity of radiotherapy should be discussed with the patient and the patient should be carefully monitored [grade D].

Frontline chemotherapy, either single-agent alkylators, anthracycline-based polychemotherapy or fludarabine-based polychemotherapy, should be chosen according to the characteristics of the patient and the disease [grade B].

Rituximab, either concurrent or sequential, should be added to frontline conventional chemotherapy [grade A]. Younger patients should not receive single-agent alkylating chemotherapy because it is not able to induce molecular remission and it reduces stem cell mobilization potential [grade C].

Interferon is not recommended as induction therapy, either alone [grade A] or in association with chemotherapy [grade A].

Molecular response should be checked at the end of first-line therapy in all patients with an informative probe who reach a complete clinical remission [grade D].

Chemotherapy or interferon is not recommended as maintenance therapy in low grade NHL [grade A]. The use of rituximab in the maintenance strategy should be considered investigational. Patients who have achieved a partial remission after first-line therapy may be considered for consolidation treatment with one of the following options: rituximab, autologous stem cell transplantation (SCT), radioimmunoconjugates (either tositumomab or ibritumomab) [grade C].

Patients not responding to first-line chemotherapy should receive further treatment provided that they are symptomatic, or have a threatened organ function, or a cytopenia secondary to bone marrow infiltration, or massive bulky disease at presentation, or steady progression over the last 6 months [grade D].

Patients not responding to first-line alkylating agent-based chemotherapy can be offered an anthracycline- and/or fludarabine-based regimen with rituximab [grade C].

Patients not responding to first line anthracycline- or fludarabine-based chemotherapy should be offered high dose chemotherapy and SCT (autologous or allogeneic) [grade B]; if SCT is not feasible it is recommended that these patients receive radioimmunoconjugates (either tositumomab or ibritumomab) [grade C].

Relapsed patients should undergo new histologic documentation prior to a decision on salvage therapy being taken [grade D].

Patients should receive further treatment provided that they are symptomatic, or have a threatened organ function, or a cytopenia secondary to bone marrow infiltration, or massive bulk at presentation, or steady progression over the preceding 6 months [grade D].

Patients who relapse after a first-line therapy not containing either anthracyclines or fludarabine should receive anthracycline- or fludarabine-based polychemotherapy associated with rituximab [grade B].

Patients under 65 years old with extended relapses after a first-line therapy containing either anthracyclines or fludarabine should be treated with high-dose therapy and autologous SCT [grade B].

Autologous SCT should be performed upon achievement of at least partial remission with an appropriate cytoreductive treatment [grade D]. It is recommended that any procedure capable of producing a lymphoma-free graft is used [grade B].

Molecular response should be checked after autologous SCT in all patients with an informative probe and a complete clinical remission [grade D]. Periodic follow-up monitoring of molecular remission after autologous SCT cannot be recommended for current clinical practice outside clinical studies [grade D].

If autologous SCT is not feasible (poor mobilization of peripheral stem cells or partial remission not achieved before SCT) and a fully matched family donor is available, it is recommended to perform allogeneic SCT [grade C].

Patients under 65 years old with a relapse after autologous SCT and a fully matched family donor should also receive allogeneic SCT [grade C].

For patients who are refractory to or relapse after autologous SCT, or for whom autologous SCT is not feasible (poor mobilization of peripheral stem cells or partial remission not achieved before SCT), but without a family donor, a search for an unrelated donor may be performed according to the indications of the National Bone Marrow Registry, provided that the patients are <55 years old [grade D].

Myeloablative allogeneic SCT should be reserved to very selected patients aged < 45 years [grade D].

Molecular response should be checked after allogeneic SCT in all patients with an informative probe and a complete clinical remission: periodic monitoring of molecular remission should be performed [grade D].

Radio-immunoconjugates are recommended for patients who relapse after anthracycline- or fludarabine-containing first-line therapy and for whom SCT is not feasible, or who relapse after SCT [grade C].

Transformed lymphoma should be treated in the same way as diffuse large cell lymphoma [grade D].

The number of bcl2⁺ circulating cells decreases after autologous SCT²⁴⁹ and patients with a molecular response to autologous SCT have an 87% lower risk of relapse,²⁵⁰⁻²⁵² the chance of relapse being proportional to the quantity of polymerase chain reaction-positive cells found in peripheral blood.²⁴⁸ A negative polymerase chain reaction status post-transplant also reduced the chance of death by 75% and was more relevant to overall survival than was the polymerase chain reaction status of the reinfused graft.²⁰⁵ Therefore, the Expert Panel deemed that the evidence was sufficient to recommend that molecular response status should be verified after completion of the transplant program. Observational studies have documented that the number of circulating bcl2⁺ cells remained stable during complete remission and increased at relapse.²⁴⁸⁻²⁵¹ However, the Expert Panel did not agree on the clinical utility of periodic monitoring of molecular remission due to the lack of direct evidence. Therefore, this strategy was deemed appropriate only in clinical trials.

Allogeneic SCT proved to have a high benefit-to-risk ratio, especially in chemosensitive young patients (for detailed analysis see previous section).^{252,253} Peripheral stem cells from sibling donors are the preferred source of hematopoietic progenitors since translated evidence from several randomized trials enrolling mixed cohorts with lymphoproliferative diseases,²⁵⁴ showed better engraftment after such transplants, without an increased risk of acute graft-versus-host disease and possible longer disease-free survival and overall survival. No randomized trial supported the superiority of reduced intensity conditioning over conventional conditioning, although retrospectively collected data on transplant-related mortality in mixed NHL cohorts might suggest such an effect.^{255,256} Further data on the possible role of alemtuzumab in conditioning regimens for allogeneic SCT are still awaited.

After allogeneic SCT for NHL, the risk of relapse is higher in patients who do not achieve a molecular response.¹⁷⁹ Even though based on evidence derived from only one non-randomized study, the Expert Panel judged it relevant to refine the prognosis of transplanted patients by assessing the molecular response status after allogeneic SCT also in routine clinical practice.

Radio-immunoconjugates are effective in relapsed patients also outside a transplantation procedure: durable responses were shown at long-term follow-up in large cohorts of patients with relapsed/ refractory follicular NHL treated with ibritumomab, tiuxetan or tositumomab.^{189,190,257} The overall response rates were 81-97% with tositumomab^{185,259,260} and 68%-89% with ibritumomab,¹⁸⁷ irrespectively of age. Complete responders maintained their response status for over 4-5 years^{185,258} and median response duration was

longer than that to the previous line of therapy, approaching 2 years in a recent update of the randomized trial with ibritumomab.^{189,190} Molecular response was also achieved in 82%-94% of the patients after radio-immunoconjugate therapy;^{261,262} however, a prolonged response in patients with a molecular response was reported only for tositumomab. Ibritumomab was also more effective than rituximab as a single-agent in a randomized trial.¹⁸⁹ Response rates to radio-immunoconjugates depended, at multivariate analysis, on the number of previous lines of treatment,¹⁸⁷ number of nodes involved and bulky disease.^{148,187,188}

Recommendations

Relapsed patients should undergo new histologic documentation prior to a decision on salvage therapy being taken [grade D].

Patients should receive further treatment provided that they are symptomatic, or have a threatened organ function, or a cytopenia secondary to bone marrow infiltration, or massive bulk at presentation, or steady progression over the preceding 6 months [grade D].

Patients who relapse after a first-line therapy not containing either anthracyclines or fludarabine should receive anthracycline- or fludarabine-based polychemotherapy associated with rituximab [grade B].

Patients under 65 years old with extended relapses after a first-line therapy containing either anthracyclines or fludarabine should be treated with high-dose therapy and autologous SCT [grade B].

Autologous SCT should be performed upon achievement of at least partial remission with an appropriate cytoreductive treatment [grade D]. It is recommended that any procedure capable of producing a lymphoma-free graft is used [grade B].

Molecular response should be checked after autologous SCT in all patients with an informative probe and a complete clinical remission [grade D]. Periodic follow-up monitoring of molecular remission after autologous SCT cannot be recommended for current clinical practice outside clinical studies [grade D].

If autologous SCT is not feasible (poor mobilization of peripheral stem cells or partial remission not achieved before SCT) and a fully matched family donor is available, it is recommended to perform allogeneic SCT [grade C]. Patients under 65 years old with a relapse after autologous SCT and a fully matched family donor should also receive allogeneic SCT [grade C].

For patients who are refractory to or relapse after autologous SCT, or for whom autologous SCT is not feasible (poor mobilization of peripheral stem cells or partial remission not achieved before SCT), but without a family donor, a search for an unrelated donor may be performed according to the indications of the National Bone Marrow Registry, provided that the patients are <55 years old [grade D].

Myeloablative allogeneic SCT should be reserved to very selected patients aged < 45 years [grade D].

Molecular response should be checked after allogeneic SCT in all patients with an informative probe and a complete clinical remission: periodic monitoring of molecular remission should be performed [grade D].

Radio-immunoconjugates are recommended for patients who relapse after anthracycline- or fludarabine-containing first-line therapy and for whom SCT is not feasible, or who relapse after SCT [grade C].

Therapy for transformed lymphoma

Histopathological transformation of low-grade follicular lymphoma to large-cell aggressive NHL is an event occurring in 15-32% of the patients.^{193,194,198} the incidence appears to reach a plateau by 6 years after the diagnosis of follicular lymphoma,^{193,195} and the median time to transformation is 66 months.¹⁹⁶ High β -2-microglobulin serum levels at diagnosis and failure to achieve complete remission after first-line therapy predict a higher risk of transformation.¹⁹³ The prognosis for transformed lymphoma is generally poor, the median survival after transformation being about 10 months^{193,197,198} thus accounting for a large proportion of deaths in patients with follicular lymphoma. Disease-free survival in transformed NHL treated with standard chemotherapy was poorer than that in *de novo* diffuse large-cell lymphoma,²⁶³ but in one study overall survival seemed better than that in primarily aggressive NHL.²⁶⁴ Young patients with limited disease who were chemosensitive experienced prolonged survival.^{193,196,265} Therefore, data did not show a relevantly different behavior between the two types of large-cell lymphoma.¹⁹⁸ Age, response to salvage therapy, B symptoms, lactate dehydrogenase values, bone marrow involvement, stage, no prior chemotherapy, and early transformation were all predictive factors for survival after transformation.^{193,196,198,266}

The median rate of overall survival after autologous SCT was reported to be 40-60% at 4-5 years,^{193,198,234,267-269} and about 30% of over 200 patients included in published series were alive without disease at 5 years.^{193,198,268-270} Survival after autologous SCT was not dissimilar to that reported for patients with non-transformed indolent NHL and primarily aggressive NHL undergoing autologous SCT.^{229,271,272} Tandem transplantation was attempted in three patients with transformed lymphoma within a series of patients with refractory/relapsed high-grade NHL:²⁷³ all the three patients were relapse-free at 32-54 months.

The literature on outcomes of allogeneic SCT in transformed indolent NHL was judged inconsistent by the Expert Panel since cases with aggressive NHL²⁷⁴ and with indolent NHL were aggregated.²⁷⁶ Successful results have been reported in selected patients, a pro-

portion of whom achieved long-term disease-free survival.^{224,276-279} The results appeared to be particularly poor for the subset of patients with both the bcl-2 and the c-myc translocations, and no effective regimen was reported.²⁷⁹⁻²⁸⁰ Conversely, high overall response rates, ranging from 50% to 80%, and an acceptable safety were reported in patients with transformed disease and <25% bone marrow involvement who were treated with ibritumomab and tositumomab,^{183,186,258} and also with rituximab therapy.¹⁵⁶

Recommendations

Transformed lymphoma should be treated in the same way as diffuse large cell lymphoma [grade D].

Discussion

In this work, a systematic review of research literature and its grading for quality provided the evidence base to be used for producing recommendations on the treatment of nodal indolent NHL (Table 2). However, to adhere to the quality standards for guideline production,^{281,282} the practice guidelines production of SIE, SIES and GITMO comprised interpretation and consensus on the evidence by the members of an Expert Panel and a consensus phase for recommendations on key clinical questions not supported by good evidence. 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. With this conceptual framework, the results of this project mostly adhered to the quality items produced by AGREE.²⁸¹ The only exceptions are that patients' views and preferences have been seldom explicitly formulated in the recommendations, a pilot application of the guideline has not been attempted and a monitoring or audit process has not been initiated. However, these guidelines have been externally reviewed by three expert radiotherapists and three senior hematologists, i.e. the presidents of the scientific societies endorsing the present guidelines. We are also aware that the potential cost implications of applying the recommendations have only been implicitly considered when formulating recommendations for high-cost drugs or procedures.

The present guidelines are focused on the most relevant clinical questions in the complex therapeutic pathway of indolent NHL, but are also aimed at supporting a rational use of novel technologies still under evaluation, such as monoclonal antibodies, radio-immunoconjugates and stem cell transplantation. The guidelines therefore cover a large domain including

the decision on how to approach first-line therapy, and the treatment of refractory, relapsed and transformed lymphoma. Furthermore, different recommendations have been formulated for diverse clinical scenarios, making the recommendations patient-specific. However, neither supportive therapy, i.e. hematopoietic growth factors, nor therapies for lymphoma-related complications, i.e. drugs for lymphoma-related autoimmune disorders, were specifically addressed by the present guidelines, since these issues belong more generally to supportive care in the field of hemato-oncology.

These guidelines agree with the NCCN guidelines,²⁸³ but are at variance with the ESMO guidelines²⁸⁴ in recommending the use of locoregional radiotherapy alone as front-line therapy for selected stage I-II patients. The Expert Panel interpreted the evidence as not supporting the use of chemotherapy in these patients. None of the studies that analyzed this issue reported a better overall survival for combined modality treatment and some studies, reporting a better progression-free survival, enrolled a large proportion of patients with aggressive lymphomas.

Both the NCCN²⁸³ and the present guidelines underline the difficulty in giving a definite recommendation on first line treatment in advanced stage indolent lymphomas so far. Many options are available for the initial treatment. Different types of chemotherapy regimens (alkylating single agent, combinations with or without anthracyclines, fludarabine-containing regimens) have been used with similar results. Thus, the choice of initial therapy largely depends on clinical factors such as age, site and extent of disease, comorbidities, pace of the disease, and the chance of future transplantation options.

The present guidelines provide specific and limited frontline treatment options for stage III-IV patients:

single-agent alkylators were reserved to the elderly patients, while younger patients were recommended not to receive this treatment in order to avoid impairment of peripheral blood stem cell mobilization for possible future salvage autologous stem cell transplantation.

The Expert Panel succeeded in providing some rules for treatment prioritization in second and further lines. In particular, candidates for autologous and allogeneic SCT are clearly defined, as are the indications for the use of radio-immunoconjugates. Finally, these guidelines fully incorporate the recent data on the use of rituximab and non-myeloablative allogeneic SCT and provide up-to-date recommendations on specific transplantation procedures. In conclusion, the SIE, SIES and GITMO guidelines represent a further effort of the scientific community to meet clinical needs and improve the quality of care for lymphoma patients.

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The members of the Expert Panel (AC, ML, MaM, AR, CT, UV, PLZ, ST) formulated the recommendations and agreed on their final version. PLZ, UV and MaM were the writing committee in charge of preparing the draft manuscript. GB and MoM contributed to the systematic literature retrieval and analysis. AC, ML, CT and ST revised the manuscript.

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