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

Giovanni Barosi
Angelo Carella
Mario Lazzarino
Monia Marchetti
Maurizio Martelli
Alessandro Rambaldi
Corrado Tarella
Umberto Vitolo
Pier Luigi Zinzani
Sante Tura

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

Haematologica 2005; 90:1236-1257

From the Laboratorio di Epidemiologia Clinica, IRCCS Policlinico S. Matteo, Pavia (GB, MM); Divisione di Ematologia e Centro Trapianti, Azienda Ospedaliera San Martino, Genova, (AC); Divisione di Ematologia, IRCCS Policlinico S.Matteo, Pavia (ML); Dipartimento di Botecnologie Cellulari ed Ematologia,Cattedra di Ematologia, Università La Sapienza, Roma (MM); Divisione di Ematologia, Spedali Riuniti, Bergamo, (AR); Cattedra di Ematologia, Azienda Ospedaliera San Giovanni Battista, Torino, (CT); Divisione di Ematologia, Azienda Ospedaliera San Giovanni Battista, Torino, (UV); Istituto di Ematologia ed Oncologia Medica "Seragnoli", Università di Bologna, Bologna, Italy (ST).

Correspondence:
Giovanni Barosi, MD,
Laboratorio di Epidemiologia Clinica,
IRCCS Policlinico S. Matteo,
viale Golgi 19, 27100, Pavia, Italy.
E-mail: barosig@smatteo.pv.it

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 produced 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 technique[10] 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 (> 5×10^9/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 Intergoup (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 interferon[19] 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 inde terminate (increased number or size of aggregates without cytological or achitectural atypia)
Partial Response (PR)	∝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 ∝ 50% in the size of previously involved nodes	Appearance of any new lesion and/or increase by ≥ 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)	∝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 wiith 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 trials[37-42] 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 Center[43-46] 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 relevent 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 Committe 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 regimens [59-61] 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 cyclophosphamide[86-88] 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 mithoxantrone 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 frontline 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 monochemotherapy 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 I^{131} 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 I^{131} 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 study[126] 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-analysis[102] 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 trial[132] 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 tositumomab[183] 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 studies[222-228] 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 survivaal, 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 indolent 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 iradiation 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 ration, 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 reports[205] 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 trial[229] 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 antracycline- 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 SCT[249] 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 reponses 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 compete 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 NHL[274] and with indolent NHL were aggregated.[276] Successful results have been reported in selected patients, a proportion 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]

Recommmendations

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 guidelines[284] 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 NCCN[283] 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.

The authors acknowledge Giampaolo Biti, Giovanni Frezza and Umberto Ricardi for their kind consultancy on the role of radiotherapy in the management of indolent NHL. The authors also thank Luca Arcaini and Nicola Lucio Liberato for their valuable support in the literature review, and Cristina Azzan for her precious contribution to the electronic repository of full-paper articles.

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.

This study was funded by Shering s.p.a., which provided the Italian Society of Hematology a grant for project expenses, reimbursement and an honorarium for the participants in the project. None of the study participants disclosed financial interest in this company. Shering s.p.a. provided financial support for the literature search, consensus conferences and secretarial personnel for this project. None of the study participants disclosed any financial interest in this company.

Manuscript received April 14, 2005. Accepted July 27, 2005.

References

1. Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E, et al. Cancer statistics, 2004. CA Cancer J Clin 2004; 54:8-29.
2. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 1998; 16:2780-95.
3. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 1997;89: 3909-18.
4. Horning SJ, Rosemberg SA. The natural history of initially untreated low-grade Non-Hodgkin's Lymphoma. N Engl J Med 1984;311:1471-5.
5. Federico M, Vitolo U, Zinzani PL, Chisesi T, Clo V, Bellesi G, et al. Prognosis of follicular lymphoma: a predictive model based on a retrospective analysis of 987 cases. Intergruppo Italiano Linfomi. Blood 2000;95:783-9.
6. Fisher RI, LeBlanc M, Press OW, Maloney DG, Miller TP. New treatment options have changed the natural history of follicular lymphoma. ASH 2004 [Abstract 583].
7. Swenson WT, Wooldridge JE, Lynch CF, Forman-Hoffman VL, Chrischilles E, Link BK. Improved survival of follicular lymphoma patients in the surveillance, epidemiology, and end-results (SEER) program. J Clin Oncol 2005; 23:5019-26.
8. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. BMJ 2001;323:334-6.
9. Williams PL, Webb C. The Delphi technique: a methodological discussion. J Adv Nurs 1994;19: 180-6.
10. Delbecq AL, van de Ven AH, Gustafson DH. Group Techniques for program planning: a guide to nominal group and Delphi processes. Scott, Foresman and Co, Glenview, IL, USA. 1975
11. Cheson BD, Bennett JM, Grever M, Kay N, Keating MJ, O'Brien S, et al. National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. Blood 1996;87:4990-7.
12. Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7: 1630-6.
13. Solal-Celigny P, Lepage E, Brousse N, Tendler CL, Brice P, Haioun C, et al. Doxorubicin containing regimen with or without interferon α2-b for advanced follicular lymphomas: final analysis of survival and toxicity in the groupe d'etudes des lymphomas folliculaires 86 trial. J Clin Oncol 1998;16: 2332-8.
14. Nathwani BN, Harris NL, Weisemburger DD, Isaacson PG, Piris MA, Berger F, et al. Follicular Lymphoma in: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissue.

Edited by Jaffe ES, Harris NL, Stein H, Vardiman JW. IARC 2001. p. 162-7.
15. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999;17:1244.
16. Anonymous. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993;329:987-94.
17. Solal-Celigny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez R, et al. Follicular lymphoma international prognostic index. Blood 2004;104: 1258-65.
18. Young RC, Longo DL, Glastein E, Ihde DC, Jaffe ES, DeVita VT. The treatment of indolent lymphomas: WW vs aggressive combined modality treatment. Semin Hematol 1988;25:11-6.
19. Brice P, Bastion Y, Lepade E, Brousse N, Haioun C, Moreau P, et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 1997;15:1110-7.
20. Ardeshna K M, Smith P, Norton A, Hancock B W, Hoskin P J, MacLennan KA, et al., on behalf of the British National Lymphoma Investigation. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. Lancet 2003; 362:516-22.
21. Soubeyran P, Eghbali H, Trojani M, Bonichon F, Richard P, Hoerni B. Is there any place for a wait-and-see policy in stage I follicular lymphoma? Ann Oncol 1996;7:713-8
22. Advani R, Rosenberg SA, Horning SJ. Stage I and II follicular non-Hodgkin's lymphoma: long-term follow-up of no initial therapy. J Clin Oncol 2004; 22: 1454-9.
23. Petersen PM, Gospodarowicz M, Tsang R, Pintilie M, Wells W, Hodgson D, et al. Long-term outcome in stage I and II follicular lymphoma following treatment with involved field radiation therapy alone. ASCO Proceedings (abstract 6521) J Clin Oncol 2004; 22: 561.
24. Gustavsson A, Osterman B, Cavallin-Stahl E. A systematic overview of radiation therapy effects in non-Hodgkin's lymphoma. Acta Oncol 2003;42:605-19.
25. Peters MV, Bush RS, Brown TC Reid J. The place of radiotherapy in the control of non-Hodgkin's lymphomata. Br. J Cancer 1975;31:386-401.
26. Chen MG, Prosnitz LR, Gonzales-Serva V, Fisher DB. Results of radiotherapy in control of stage I and Il non-Hodgkin's lymphoma. Cancer 1979; 43:1245-54.
27. Gospodarowicz MK, Bush RS, Brown TC, Chua T. Prognostic factors in nodular lymphomas: a multivariate analysis based on the Princess Margaret Hospital experience. Int J Radiat Oncol Biol Phys 1984;10:489-97.
28. Gomez GA, Barcos M, Krishnamsetty RM, Panahon AM, Han T, Henderson ES. Treatment of early-stages I and II nodular, poorly-differentiated lymphocytic lymphomas. Am J Clin Oncol 1986; 9:40-4.
29. Lawrence TS, Urba WJ, Steinberg SM, Sundeen JT, Cossman J, Young RC, et al. Retrospective analysis of stage I and II indolent lymphomas at the National Cancer Institute. Int J Radiat Oncol Biol Phys 1988;14:417-24.
30. Soubeyran P, Eghbali H, Bonichon F, Coindre JM, Richaud P, Hoerni B. Localized follicular lymphomas: prognosis and survival of stages I and II in a retrospective series of 103 patients. Radiother Oncol 1988;13:91-8
31. Richards MA, Gregory WM, Hall PA, Dhaliwal HS, Fernandez J, Stansfeld AG, et al. Management of localized non-Hodgkin's lymphoma: The experience of St Bartholomew's Hospital 1972-1985. Hematol Oncol 1989; 7:1-18.
32. Epelbaum R, Kuten A, Coachman NN, Faraggi D, Ben-Arie Y, Ben-Shahar M, et al. Stage I-II low grade non-Hodgkin's lymphoma: Prognostic factors and treatment results. Strahlenther Onkol 1992;168:66-71.
33. Vaughan Hudson B, Vaughan Hudson G, LacLennan KA, Anderson L, Linch DC. Clinical stage I non-.Hodgkin's lymphoma: long term follow up of patients treated by the British National Lymphoma Investigation with radiotherapy alone as initial therapy. Br J Cancer 1994;69:1088-93
34. MacManus MP, Hoppe RT. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term study of patients treated at Stanford University. J Clin Oncol 1996; 14:1282-90.
35. Kamath SS, Marcus RB, Lynch JW, Mendenhall NP. The impact of radiotherapy dose and other treatment-related and clinical factors on in-field control in stage I and II non-Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 1999;44:563-8.
36. Wilder RB, Jones D, Tucker SL, Fuller LM, Ha CS, McLaughlin P, et al. Long-term results with radiotherapy for Stage I-II follicular lymphomas. Int J Radiat Oncol Biol Phys 2001;51:1219-27.
37. Landberg TG, Hakansson LG, Moller TR, Mattsson WK, Landys KE, Johansson BG, et al. CVP-remission-maintenance in stage I or II non-Hodgkin's lymphomas: preliminary results of a randomized study. Cancer 1979;44: 831-8.
38. Yahalom J, Varsos G, Fuks Z, Myers J, Clarkson BD, Straus DJ. Adjuvant cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy after radiation therapy in stage I low-grade and intermediate-grade non-Hodgkin lymphoma. Results of a prospective randomized study. Cancer 1993;71:2342-50.
39. Nissen NI, Ersboll J, Hansen HS, Walbom-Jorgensen S, Pedersen-Bjegaard J, Hansen MM, et al. A randomized study of radiotherapy versus radiotherapy plus chemotherapy in stage I-II non-Hodgkin's lymphomas. Cancer 1983;52:1-7
40. Carde P, Burgers JM, van Glabbeke M, Hayat M, Cosset JM, Somers R, et al. Combined radiotherapy-chemotherapy for early stages non-Hodgkin's lymphoma: the 1975-1980 EORTC controlled lymphoma trial. Radiother Oncol 1984;2:301-12.
41. Monfardini S, Banfi A, Bonadonna G, Rilke F, Milani F, Valagussa P, Lattuada A. Improved five year survival after combined radiotherapy-chemotherapy for stage I-II non-Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 1980;6:125-34.
42. Kelsey SM, Newland AC, Hudson GV, Jelliffe AM. A British National Lymphoma Investigation randomised trial of single agent chlorambucil plus radiotherapy versus radiotherapy alone in low grade, localised non-Hodgkins lymphoma. Med Oncol 1994;11:19-25.
43. Mc Laughlin P, Fuller LM, Velasquez WS, Sullivan-Halley JA, Butler JJ, Cabanillas F. Stage I-II follicular lymphoma. Treatment results for 76 patients. Cancer 1986;58:1596-602.
44. Mc Laughlin P, Fuller LM, Redman J, Hagemeister F, Durr E, Allen P, et al. Stage I-II low-grade lymphomas: a prospective trial of combination chemotherapy and radiotherapy. Ann Oncol 1991;2 Suppl 2:137-40.
45. Besa PC, Mc Laughlin PW, Cox JD, Fuller LM. Long term assessment of patterns of treatment failure and survival in patients with stage I or II follicular lymphoma. Cancer 1995;75:2361-7.
46. Seymour JF, Pro B, Fuller LM, Manning JT, Hagemeister FB, Romaguera J, et al. Long-term follow-up of a prospective study of combined modality therapy for stage I-II indolent non-Hodgkin's lymphoma. J Clin Oncol 2003;21: 2115-22.
47. Jacobs JP, Murray CJ, Scultz JF, Wilson JF, Gosowitz MS, Cox JD. Central lymphatic irradiation for stage III nodular malignant lymphoma: long term results. J Clin Oncol 1993;11:233-8.
48. De Los Santos JF, Mendenhall NP, Lynch JW Jr. Is comprehensive lymphatic irradiation for low grade non Hodgkin lymphoma curative therapy? Long term experience as a single institution. Int J Radiat Oncol Biol Phys 1997;38:3-8.
49. Murtha AD, Knox SA, Hoppe RT, Rupnov BA, Hanson JH. Long-term follow-up of patients with stage III follicular lymphoma treated with primary radiotherapy at Stanford University. Int J Radiat Oncol Biol Phys 2001;49:3-15.
50. Ha CS, Kong JS, McLaughlin P, Tucker SL, Fayad LE, Hess MA, et al. Stage III follicular lymphoma: long-term follow-up and patterns of failure. Int J Radiat Oncol Biol Phys 2003;57:748-54.
51. Ha CS, Cabanillas F, Lee MS, Tucker SL, McLaughlin P, Rodriguez MA, et al. A prospective randomized study to compare the molecular response rates between central lymphatic irradiation (CLI) and intensive alternating triple chemotherapy (ATT) in the treatment of stage I-III follicular lymphoma. Int J Radiat Oncol Biol Phys 2003;57:S211-2.
52. Chisesi T, Congiu M, Contu A, Coser P, Moretti L, Porcellini A, et al. Randomized study of chlorambucil (CB) compared to interferon (α-2b) combined with CB in low-grade non-Hodgkin's lymphoma: an interim report of a randomized study. Non-Hodgkin's Lymphoma Cooperative Study Group. Eur J Cancer 1991; Suppl 4:31-3.
53. Price CG, Rohatiner AZ, Steward W, Deakin B, Bailey N, Norton A, et al. Interferon α-2b in addition to chlorambucil in the treatment of follicular lym-

phoma: preliminary results of a randomized trial in progress. Eur J Cancer 1991; Suppl 4:34-6.
54. Ezdinli EZ, Anderson JR, Melvin F, Glick JH, Davis TE, O'Connell MJ. Moderate versus aggressive chemotherapy of nodular lymphocytic poorly differentiated lymphoma. J Clin Oncol 1985; 3:769-75.
55. Glick JH, Barnes JM, Exdinli EZ, Berard CW, Orlow EL, Bennett JM. Nodular mixed lymphoma: results of a randomized trial failing to confirm prolonged disease-free survival with COPP chemotherapy. Blood 1981;58:920-5.
56. Lister TA, Cullen MH, Beard ME, Brearley RL, Whitehouse JM, Wrigley PF, et al. Comparison of combined and single-agent chemotherapy in non-Hodgkin's lymphoma of favourable histological type. Br Med J 1978;1:533-7.
57. Hayhoe FG. Chemotherapy in the management of stage III/IV grade 1 non-Hodgkin's lymphomas (report no 17). Clin Radiol 1981;32:547-52.
58. Unterhalt M, Herrmann R, Tiemann M, Parwaresch R, Stein H, Trumper L, et al. Prednimustine, mitoxantrone (PmM) vs cyclophosphamide, vincristine, prednisone (COP) for the treatment of advanced low-grade non-Hodgkin's lymphoma. German Low-Grade Lymphoma Study Group. Leukemia 1996;10:836-43.
59. Baldini L, Brugiatelli M, Luminari S, Lombardo M, Merli F, Sacchi S, et al. Treatment of indolent B-Cell nonfollicular lymphomas: final results of the LL01 randomized trial of the Gruppo Italiano per lo Studio dei Linfomi. J Clin Oncol 2003;21:1459-65.
60. Peterson BA, Petroni GR, Frizzera G, Barcos M, Bloomfield CD, Nissen NI, et al. Prolonged single-agent versus combination chemotherapy in indolent follicular lymphomas: a study of the Cancer and Leukemia Group B. J Clin Oncol 2003;21:5-15.
61. Kimby E, Bjorkholm M, Gahrton G. Glimelius B, Hagberg H, Johansson B, et al. Chlorambucil/prednisone vs. CHOP in symptomatic low-grade non-Hodgkin's lymphomas: a randomized trial from the Lymphoma Group of Central Sweden. Ann Oncol 1994;5: 67-71.
62. Brandt L, Kimby E, Nygren P, Grimelius B. A systematic overview of chemotherapy effects in indolent non-Hodgkin's lymphoma. Acta Oncol 2001;40:213-23.
63. Haas R, Moos M, Mohle R, Dohner H, Witt B, Goldschmidt H, Murea S, et al. High-dose therapy with peripheral blood progenitor cell transplantation in low-grade non-Hodgkin's lymphoma. Bone Marrow Transplant. 1996;17: 149-55.
64. Haas R, Mohle R, Fruhauf S, Goldschmidt H, Witt B, Flentje M, et al. Patient characteristics associated with successful mobilizing and autografting of peripheral blood progenitor cells in malignant lymphoma. Blood 1994; 83:3787-94.
65. Jones SE, Grozea PN, Milelr TP, Van Slyck EJ, Balcerzak SP, Costanzi JJ, et al. Chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone alone or with levamisole or with levamisole plus BCG for malignant lymphoma: a Southwest Oncology Group Study. J Clin Oncol 1985;3:1318-24.
66. Dana BW, Dahlberg S, Nathwani BN, Chase E, Coltman C, Miller TP, et al. Long-term follow-up of patients with low-grade malignant lymphomas treated with doxorubicin-based chemotherapy or chemoimmunotherapy. J Clin Oncol 1993;11:644-51
67. Hovgaard DJ, Nissen NI. Effects of interleukin-3 following chemotherapy of non-Hodgkin's lymphoma. A prospective, controlled phase I/II study. Eur J Haematol 1995;54:78-84.
68. Rambaldi A, Lazzari M, Manzoni C, Carlotti E, Arcaini L, Baccarani M, et al. Monitoring of minimal residual disease after CHOP and Rituximab in previously untreated patients with follicular lymphoma. Blood 2002;99:856-62.
69. Jaeger G, Neumeister P, Brezinschek R, Hofler G, Quehenberger F, Linkesch W, et al. Rituximab (anti-CD20 monoclonal antibody) as consolidation of first-line CHOP chemotherapy in patients with follicular lymphoma: a phase II study. Eur J Haematol 2002; 69:21-26.
70. Pan I, Qin I, Farber C, O'Brien J, Filippa D, Portlock CS. CHOP with high dose cyclophosphamide consolidation versus CHOP alone as initial therapy for advanced stage, indolent non-Hodgkin's lymphomas. Leuk Lymphoma 2003;44: 967-71.
71. McKelvey EM, Gottlieb JA, Wilson HE, Haut A, Talley RW, Stephens R, et al. Hydroxyldaunomycin (adriamycin) combination chemotherapy in malignant lymphoma. Hematol Oncol 1976; 38:1484-93.
72. McLaughlin P, Cabanillas F, Hagemeister FB, Swan F Jr, Romaguera JE, Taylor S, et al. CHOP-Bleo plus interferon for stage IV low-grade lymphoma. Ann Oncol 1993;4:205-11.
73. Bernard T, Johnson SA, Prentice AG, Jones L, Phillips MJ, Newland AC. Mitoxantrone, chlorambucil and prednisolone in the treatment of non-Hodgkin's lymphoma. Leuk Lymphoma 1994;15:481-5.
74. Lombardo M, Morabito F, Merli F, Molica S, Cavanna L, Sacchi S, et al. Bleomycin, epidoxorubicin, cyclophosphamide, vincristine and prednisone (BACOP) in patients with follicular non-Hodgkin's lymphoma: results of a prospective, multicenter study of the Gruppo Italiano Per Lo Studio Dei Linfomi (GISL). Leuk Lymphoma 2002; 43:1795-801.
75. Fisher RI, Dana BW, LeBalnc M, Kjeldsberg C, Forman JD, Unger JM, et al. Interferon α consolidation after intensive chemotherapy does not prolong the progression-free survival of patients with low-grade non-Hodgkin's lymphoma: results of the Southwest Oncology Group randomized phase III study 8809. J Clin Oncol 2000; 18:2010-6.
76. Smalley RV, Weller E, Hawkins MJ, Oken MM, O'Connell MJ, Haase-Statz S, et al. Final analysis of the ECOG I-COPA trial (E6484) in patients with non-Hodgkin's lymphoma treated with interferon a (IFN-α2a) plus an anthracycline-based induction regimen. Leukemia 2001;15:1118-22.
77. Zinzani PL. Non-Hodgkin's lymphoma: the evolving role of purine analogues. Best Practice Res Clin Haematol 2002; 15:505-16.
78. Solal-Celigny P, Brice P, Brousse N, Caspard H, Bastion Y, Haioun C, et al. Phase II trial of fludarabine monophosphate as first-line treatment in patients with advanced follicular lymphoma: a multicenter study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 1996;14:514-9.
79. Coiffier B, Neidhardt-Berard EM, Tilly H, Belanger C, Bouabdallah R, Haioun C, et al. Fludarabine alone compared to CHVP plus interferon in elederly patients with follicular lymphoma and adverse prognostic parameters: a GELA study. Ann Oncol 1999;10:1191-7.
80. Hagenbeek A, Eghbali H, Monfardini S, Resegotti E, Hoskin J, de Wolf-Peeters C, et al. Fludarabine compared with CVP chemotherapy in newly diagnosed patients with stages III and IV low grade malignant non-Hodgkin's lymphoma. Final analysis of a prospective randomized phase III intergroup study in 381 patients. ASH 2001. Blood 2001; 98:843a[abstract 3501].
81. Zinzani PL, Magagnoli M, Moretti L, De Renzo A, Battista R, Zaccaria A, et al. Randomized trial of fludarabine versus fludarabine and idarubicin as frontline treatment in patients with indolent or mantle-cell lymphoma. J Clin Oncol 2000;18:773-9.
82. Zinzani PL, Magagnoli M, Bendandi M, Gherlinzoni F, Orcioni GF, Cellini C, et al. Efficacy of fludarabine and mitoxantrone (FN) combination regimen in untreated indolent non-Hodgkin's lymphomas. Ann Oncol 2000;11:363-5.
83. Velasquez WS, Lew D, Grogan TM, Spiridonidis CH, Balcerzak SP, Dakhil SR, et al. Combination of fludarabine and mitoxantrone in untreatedsStages III and IV low-grade lymphoma: S9501. J Clin Oncol 2003;21:1996-2003.
84. McLaughlin P, Hagemeister FB, Romaguera JE, et al. Fludarabine, Mitoxantrone and dexamethasone : an effective new regimen for indolent lymphoma. Blood 1998, 91:2955-60.
85. Vitolo U, Boccomini C, Astolfi M, Ladetto M, Rota-Scalbrini D, Pogliani E, et al. High clinical and molecular response rate in elderly patients with advanced stage follicular lymhoma treated at diagnosis with a brief chemo-immunotherapy FND + rituximab. Blood 2003;2:10298:[abstract 1452392].
86. Zinzani PL, Pulsoni A, Perrotti A, Soverini S, Zaja F, De Renzo A, et al. Fludarabine plus mitoxantrone with and without Rituximab versus CHOP with and without Rituximab as frontline treatment for patients with follicular lymphoma. J Clin Oncol 2004;22: 2654-61.
87. Hochster HS, Oken MM, Winter JN, Gordon LI, Raphael BG, Bennett JM, et al. Phase I study of fludarabine plus cyclophosphamide in patients with previously untreated low-grade lymphoma: results and and long-term follow-up--a report from the Eastern Cooperative Oncology Group. J Clin Oncol 2000; 18:987-94.
88. Flinn IW, Byrd JC, Morrison C, Jamison J, Diehl LF, Murphy T, et al. Fludarabine and cyclophosphamide with filgrastim support in patients with previously untreated indolent lymphoid malignancies. Blood 2000;96:71-5.
89. Tsimberidou AM, McLaughlin P, Younes A, Rodriguez MA, Hagemeister FB, Sarris A, et al. Fludarabine, mitoxantrone, dexamethasone (FND) compared with an alternating triple therapy (ATT) regimen in patients

with stage IV indolent lymphoma. Blood 2002; 100:4351-7
90. Foussard C, Colombat P, Maisonneuve H, Berthou C, Gressin R, Rousselet MC, et al. Long-term follow-up of a randomized trial of fludarabine-mitoxantrone, compared with cyclophosphamide, doxorubicin, vindesine, prednisone 8CHVP), as first-line treatment of elderly patients with advanced, low-grade non-Hodgkin's lymphoma before the era of monoclonal antibodies. Ann Oncol 2005;16: 466-72.
91. Tam CS, Wolf MM, Januszewicz EH, Grigg AP, Prince HM, Westerman D, Seymour JF. A new model for predicting infectious complications during fludarabine-based combination chemotherapy among patients with indolent lymphoid malignancies. Cancer 2004;101:2042-9.
92. Byrd JC, Hargis JB, Kester KE, Hospenthal DR, Knutson SW, Diehl LF. Opportunistic pulmonary infections with fludarabine in previously treated patients with low-grade lymphoid malignancies: a role for Pneumocystis carinii pneumonia prophylaxis. Am J Hematol 1995;49:135-42.
93. Visani G, Lemoli RM, Tosi P, Martinelli G, Testoni N, Ricci P, et al. Fludarabine-containing regimens severely impair peripheral blood stem cells mobilization and collection in acute myeloid leukaemia patients. Br J Haematol 1999; 105:775-9.
94. Tournilhac O, Cazin B, Lepretre S, Divine M, Maloum K, Delmer A, et al. Impact of frontline fludarabine and cyclophosphamide combined treatment on peripheral blood stem cell mobilization in B-cell chronic lymphocytic leukemia. Blood 2004;103:363-5.
95. Morgan SJ, Seymour JF, Grigg A, Matthews JP, Prince HM, Wolf MM, et al. Predictive factors for successful stem cell mobilization in patients with indolent lymphoproliferative disorders previously treated with fludarabine. Leukemia 2004;18:1034-8.
96. Rohatiner A, Radford J, Deakin D, Earl H, Love SB, Price O, et al. A randomized controlled trial to evacuate the role of intereferon as initial and maintenance therapy in patients with follicular lymphoma. Br J Cancer 2001;85: 29-35.
97. Peterson BA, Petroni GR, Oken MM, Johnson JL, Barcos M, Copper MR. Cyclophosphamide versus cyclophosphamide plus interferon a-2b in follicular low-grade lymphomas: an intergroup phase III trial (CALGB 8691 and EST 7486). J Clin Oncol 1997;16 Suppl 1:14.
98. Arranz R, Garcia-Alonso P, Sobrino P, Zamora P, Carrion R, Garcia-Larana J, et al. Role of interferon a-2b in the induction and maintenance treatment of low-grade non-Hodgkin's lymphoma: results from a prospective, multicenter trial with double randomisation. J Clin Oncol 1998;16:1538-46.
99. Smalley RV, Andersen JW, Hawkins MJ, Bhide V, O'Connell MJ, Oken MM, et al. Interferon a combined with cytotoxic chemotherapy for patients with non-Hodgkin's lymphoma. N Engl J Med 1992;327:1336-41.
100. Allen IE, Ross SD, Borden SP, Monroe MW, Kupelnick B, Connelly JE, et al. Meta-analysis to assess the efficacy of interferon-α in patients with follicular non-Hodgkin's lymphoma. J Immunother 2001;24:58-65.
101. Rohatiner W, Gregory B, Peterson B, Smalley R, Solal-Celigny P, Hagenbeek A, et al. A meta-analysis (MA) of randomised trials evaluating the role of interferon (IFN) as treatment for follicular lymphoma. J Clin Oncol 1998;17 Suppl 1:4.
102. Rohatiner AZ, Gregory WM, Peterson B, Borden E, Solal-Celigny P, Hagenbeek A, et al. Meta-analysis to evaluate the role of interferon in follicular lymphoma. J Clin Oncol 2005;23:2215-23.
103. Cole BF, Solal-Celigny P, Gelber RD, Lepage E, Gisselbrecht C, Reyes F , et al. Quality-of-life-adjusted survival analysis of interferon α-2b treatment for advanced follicular lymphoma: an aid to clinical decision making. J Clin Oncol 1998;16:2339-44.
104. Wirt DP, Giles FJ, Oken MM, Solal-Celigny P, Beck JR. Cost-Effectiveness of interferon α-2b added to chemotherapy for high-tumor-burden follicular non- Hodgkin's lymphoma. Leuk Lymphoma 2001;40:565-79.
105. Ghielmini M, Schmitz S-F H, Cogliatti S, Pichert G, Fey M, Betticher D, et al. Prolonged treatment with rituximab significantly improves event free survival and duration of response in patients with follicular Lymphoma: a randomised SAKK Trial. Blood 2002; 100:161a[Abstract 604].
106. Solal-Céligny P, Salles G, Brousse P, Soubeyran P, Delwail V, Deconninck E, et al. Updated results of Rituximab as single first-line therapy for patients with follicular lymphoma (FL) and a low tumor burden: clinical and molecular evaluation. Ann Oncol 2002;13 Suppl [Abstract 506].
107. Witzig TE, Vukov AM, Habermann TM, Geyer S, Kurtin PJ, Friedenberg WR, et al. Rituximab therapy for patients with newly diagnosed, advanced-stage, follicular grade I non-Hodgkin's lymphoma: a phase II trial in the North Central Cancer Treatment Group. J Clin Oncol 2005;23:1103-8.
108. Baltazar S, Tripp G, Baez E, Rivas S, Solis L, Ignacio G, et al. CNOP vs. CNOP-rituximab vs. rituximab alone as first-line therapy for indolent non-Hodgkin lymphoma (INHL): preliminary diseasefree/overall survival analysis. Hematol J 2004;5: Suppl 10 [abstract 028].
109. Marcus R, Imrie K, Belch A, Cunningham D, Flores E, Catalano J, et al. CVP chemotherapy plus Rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 2005;105:1417-23
110. Hiddemann W, Dreyling MH, Forstpointner R, Kneba M, Woermann B, Lengfelder E, et al. Combined Immuno-Chemotherapy (R-CHOP) dignificantly improves time to treatment failure in first line therapy of follicular lymphoma. Results of a prospective randomized Trial of the German Low Grade Lymphoma Study Group (GLSG). Blood 2003; 102:104a abstract 352.
111. Salles GA, Foussard C, Nicolas M, Franck M, Chantal D, Thierry L, et al. Rituximab added to αIFN+CHVP improves the outcome of follicular lymphoma patients with a high tumor burden: first analysis of the GELA-GOELAMS FL-2000 randomized trial in 359 patients. ASH 2004[abstract 160].
112. Herold M, Pasold R, Srock S, Neser S, Niederwieser D, Neubauer A, et al. Results of a prospective randomised open label phase III study comparing rituximab plus mitoxantrone, chlorambucile, prednisolone chemotherapy (R-MCP) versus MCP alone in untreated advanced indolent non-Hodgkin's lymphoma (NHL) and mantle-cell-lymphoma (MCL). ASH 2004 (abstract 584)
113. Czuczman MS, Weaver R, Alkuzweny B, Berlfein J, Grillo-Lopez AJ. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. J Clin Oncol 2004; 22:4711-6.
114. Czuczman MS, Koryzna A, Mohr A, Stewart C, Donohue K, Blumenson L, et al. Rituximab in combination with fludarabine chemotherapy in low-grade or follicular lymphoma. J Clin Oncol 2005; 23:694-704.
115. Hainsworth JD, Litchy S, Shaffer DW, Lackey VL, Grimaldi M, Greco FA. Maximizing therapeutic benefit of rituximab: maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma--a randomized phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 2005;23:1088-95.
116. Kaminski MS, Tuck M, Estes J, Kolstad A, Ross CW, Zasadny K, et al. 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 2005;352:441-9.
117. Leonard JP, Coleman M, Kostakoglu L, Chadburn A, Fiore JM, Furman RR, et al. Durable remissions from fludarabine followed by the iodine I-131 tositumomab Bexxar therapeutic regimen for patients with previously untreated follicular non-Hodgkin's lymphoma (NHL).[Abstract 6518].
118. Link B, Kaminski MS, Coleman M, Leonard JP. Phase II study of CVP followed by tositumomab and iodine I 131 tositumomab (Bexxar therapeutic regimen) in patients with untreated follicular non-Hodgkin's lymphoma (NHL). ASCO 2004[Abstract 6520].
119. Shipley DL, Spigel DR, Carrell DL, Dannaher C, Greco FA, Hainsworth DJ. Phase II trial of Rituximab and short duration chemotherapy followed by 90Y-ibritumomab tiuxetan as first-line treatment for patients with follicular lymphoma: a Minnie Pearl Cancer Research Network phase II trial. ASCO 2004[Abstract 6519].
120. Sebban C, Belanger C, Brousse N, Mounier N, Brice P, Haioun C, et al. Comparison of CHVP + interferon with CHOP followed by autologous stem cell transplantation with a TBI conditioning regimen in untreated patients with high tumor burden follicular lymphoma: results of the randomized GELF94 trial (G.E.L.A. Study Group). Blood 2003 [Abstract 354].
121. Deconinck E, Foussard C, Milpied N, Bertrand PP, Michenet P, Cornillet-LeFebvre P, et al. High-dose therapy followed by autologous purged stem-cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by the GOELAMS. Blood 2005;105:3817-23
122. Lenz G, Dreyling M, Schiegnitz E, Forstpointner R, Wandt H, Freund M, Hess G, et al. Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression-free survival

in follicular lymphoma - results of a prospective randomized trial of the German low grade lymphoma study group (GLSG). Blood 2004 ;104:2667-74.
123. Rambaldi A, Carlotti E, Oldani E, Della Starza I, Baccarani M, Cortelazzo S, et al. Quantitative PCR of bone marrow BCL2/IgH positive cells at diagnosis predicts treatment response and long-term outcome in follicular non Hodgkin's lymphoma. Blood 2005; 105: 3428-33.
124. Mandigers CM, Meijerink JP, Mensink EJ, Tonnissen EL, Hebeda KM, Bogman MJ, et al. Lack of correlation between numbers of circulating t(14;18)-positive cells and response to first-line treatment in follicular lymphoma. Blood 2001;98:940-4.
125. Hagenbeek A, Carde P, Meerwaldt JH, Somers R, Thomas J, De Bock R, et al. Maintenance of remission with human recombinant interferon α-2a in patients with stages III and IV low-grade malignant non-Hodgkin's lymphoma. J Clin Oncol 1998;16:41-7
126. Aviles A, Duque G, Talavera A, Guzamn R. Interferon α2b as maintenance therapy in low grade malignant lymphoma improves duration of remission and survival. Leuk Lymphoma 1996;20:495-9.
127. Unterhalt M, Hermann R, Koch P, Trümper L, Bodenstein H, Dietzfelbinger H et al. Long term interferon alpha maintenance prolongs remission duration in advanced low grade lymphomas and is related to the efficacy of initial cytoreductive chemotherapy. Blood 1996;88:453a [Abstract 1801].
128. Unterhalt M, Herrmann R, Nahler M, Trümper L, Bodenstein H, Landys K et al. Significant prolongation of disease free survival in advanced low grade non Hodgkin lymphomas (NHL) by interferon alpha maintenance. Blood 1995;86:439[Abstract 1744].
129. Dana BW, Unger J, Fisher RI. A randomized study of a-interferon consolidation in patients with low-grade lymphoma who have responded to PRO-MACE-MOPP (day 1-8) (SWOG 8809). Proc Am Soc Clin Oncol 1998;17:3a abstract 10.
130. Piro LD, White CA, Grillo-Lopez AJ, Janakiraman N, Saven A, Beck TM, et al. Extended rituximab (anti-CD20 monoclonal antibody) therapy for relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma. Ann Oncol 1999;10:655-61.
131. Hainsworth JD, Litchy S, Barton JH, Houston GA, Hermann RC, Bradof JE, et al. Single-agent Rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: a phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 2003; 21:1746-51.
132. Ghielmini M, Schmitz SF, Cogliatti SB, Pichert G, Hummerjohann J, Waltzer U, et al. Prolonged treatment with Rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x4 schedule. Blood 2004;103: 4416-23.
133. Hochster HS, Weller E, Ryan T, Habermann TM, Gascoyne R, Frankel SR, et al. Results of E1496: a phase III trial of CVP with or without maintenance rituximab in advanced indolent lymphoma (NHL). J Clin Oncol 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 22 [abstract 6502].
134. Davis TA, Maloney DG, Grillo-Lopez AJ, White CA, Williams ME, Weiner GJ, et al. Combination immunotherapy of relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma with Rituximab and interferon-α-2a. Clin Cancer Res 2000;6:2644-52.
135. Sacchi S, Federico M, Vitolo U, Boccomini C, Vallisa D, Baldini, et al. Clinical activity and safety of combination immunotherapy with IFN-α 2a and Rituximab in patients with relapsed low grade non-Hodgkin's lymphoma. Haematologica 2001;86: 951-8.
136. Morschhauser F, Recher C, Galoin S, Milpied N, Gressin R, Salles G, et al. Morschhauser2002ASCO Multicenter, phase II trial to evaluate the efficacy and safety of Rituximab in patients suffering from follicular non-Hodgkin's lymphoma (FNHL) with residual minimal disease after autologous transplantation of hematopoietic stem cell (M39012 trial). ASCO 38th Annual Meeting Orlando, Fl., abstract 1066.
137. Arcaini L, Orlandi E, Alessandrino EP, Iacona I, Brusamolino E, Bonfichi M, et al. A model of in vivo purging with rituximab and high-dose AraC in follicular and mantle cell lymphoma. Bone Marrow Transplant 2004;34:175-9.
138. Ezdinli EZ, Harrington DP, Kucuk O, Silverstein MW, Anderson J, O'Connell MJ. The effect of intensive intermittent maintenance therapy in advanced low-grade non-Hodgkin's lymphoma. Cancer 1987;60:156-60.
139. Steward WP, Crowther D, McWilliam LJ, Jones JM, Deakin DP, Todd ID, et al. Maintenance chlorambucil after CVP in the management of advanced stage, low-grade histologic type non-Hodgkin's lymphoma. A randomized prospective study with an assessment of prognostic factor. Cancer 1988;61: 441-7.
140. Cabanillas F, Hagemeister FB, Bodey GP, Freireich EJ. IMVP-16: an effective regimen for patients with lymphoma who have relapsed after initial combination chemotherapy. Blood 1982;60: 693-7.
141. McLaughlin P, Hagemeister FB, Romaguera JE, Sarris AH, Pate O, Younes A, et al. Fludarabine, mitoxantrone, and dexamethasone: an effective new regimen for indolent lymphoma. J Clin Oncol 1996;14:1262-8.
142. Rodriguez-Monge EJ, Cabanillas F. Long-term follow-up of platinum-based lymphoma salvage regimens. The M.D. Anderson Cancer Center experience. Hematol Oncol Clin North Am 1997; 11:937-47.
143. Cohen A, Polliack A, Ben-Bassat I, Avigdor A, Bennett M, Berkowicz M, et al. Results of a phase II study employing a combination of fludarabine, cyclophosphamide and Ruximab (FCR) as primary therapy for patients with advanced follicular lymphoma (FL): The Israel Cooperative Lymphoma Group. Blood 2002;100: 360a [abstract 1393].
144. Gregory SA, Venugopal P, Adler S, Enschede S, Yunus F, O'Brien T, et al. Combined fludarabine, mitoxantrone, and Ruximab achieves a high response as initial treatment for advanced low grade non-Hodgkin's lymphoma (LGNHL). Blood 2002; 100:362a [abstract 1401].
145. Vitolo U, Boccomini C, Astolfi M, Ladetto M, Rota-Scalbrini D, Pogliani E, et al. High clinical and molecular response rate in elderly patients with advanced stage follicular lymhoma treated at diagnosis with a brief chemo-immunotherapy FND + rituximab. Blood 2002;100:359a [abstract 1392].
146. Lenz G, Unterhalt M, Haferlach T, Hiddeman W, Dreyling MH. Significant increase of secondary myelodysplasia and acute myeloid leukemia after myeloablative radiochemotherapy followed by autologous stem cell transplantation in indolent lymphoma patients. Results of a prospective randomized study for the GLSG. Blood 2003;102:986a [Abstract 3671].
147. Press OW, Unger JM, Braziel RM, Maloney DG, Miller TP, LeBlanc M, et al. A Phase II Trial of CHOP chemotherapy followed by tositumomab/iodine I131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: Southwest Oncology Group protocol S9911. Blood 2003;102:1606-12.
148. Witzig TE, Gordon LI, Cabanillas F, Czuczman MS, Emmanouilides C, Joyce R, Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus Rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002;15;20:2453-63.
149. Foran JM, Gupta RK, Cunningham D, Popescu RA, Goldstone AH, Sweetenham JW, et al. A UK multicentre phase II study of Rituximab (chimaeric anti-CD20 monoclonal antibody) in patients with follicular lymphoma, with PCR monitoring of molecular response. Br J Haematol 2000; 109:81-8
150. Czuczman MS, Grillo-Lopez AJ, White CA, Saleh M, Gordon L, Lo Buglio AF, et al. Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. J Clin Oncol 1999; 17:268-76.
151. Forstpointner R, Dreyling M, Repp R, Hermann S, Haenel A, Metzner B, et al. The addition of Rituximab to a combination of fludarabine, cyclophophamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared to FCM alone in patients with relapsed and refractory follicualr and mantle cell lymphomas - results of a prospective randomized study of the German low grade lymphoma study group (GLSG). Blood 2004;104:3064-71.
152. Herold M, Fiedler F, Pasold R, Srock S, Knauf W, Freund M, Naumann R, et al. Efficacy and toxicity of Rituximab plus MCP versus MCP alone in advanced indolent NHL - Interim results of a clinical phase III study of the East German Study Group Hematology/Oncology (OSHO). ICML 2002 (abstract 511).
153. Magni M, Di Nicola M, Devizzi L, Matteucci P, Lombardi F, Gandola L, et al. Successful in vivo purging of CD34-containing peripheral blood harvests in mantle cell and indolent lymphoma: evidence for a role of both chemotherapy and Rituximab infusion. Blood 2000; 96:864-9

154. Perry AR, Watts MJ, Peniket AJ, Goldstone AH, Linch DC. Progenitor cell yields are frequently poor in patients with histologically indolent lymphomas especially when mobilized within 6 months of previous chemotherapy. Bone Marrow Transplant 1998;21:1201-5.
155. McQuaker IG, Haynes AP, Anderson S, Stainer C, Owen RG, Morgan GJ, et al. Engraftment and molecular monitoring of CD34+ peripheral-blood stem-cell transplants for follicular lymphoma: a pilot study. J Clin Oncol 1997;15:2288-95.
156. Bensinger W, Appelbaum F, Rowley S, Storb R, Sanders J, Lilleby K, et al. Factors that influence collection and engraftment of autologous peripheral-blood stem cells. J Clin Oncol 1995; 13: 2547-55.
157. Vantelon JM, Koscielny S, Brault P, Bourhis JH, Ribrag V, Pico J, et al. Scoring system for the prediction of successful peripheral blood stem cell (PBSC) collection in non-Hodgkin's lymphoma (NHL): application in clinical practice. Bone Marrow Transplant 2000;25:495-9.
158. Bastion Y, Brice P, Haioun C, Sonet A, Salles G, Marolleau JP, et al. Intensive therapy with peripheral blood progenitor cell transplantation in 60 patients with poor-prognosis follicular lymphoma. Blood 1995;86:3257-62.
159. Voso MT, Martin S, Hohaus S, Abdallah A, Schlenk RF, Ho AD, et al. Prognostic factors for the clinical outcome of patients with follicular lymphoma following high-dose therapy and peripheral blood stem cell transplantation (PBSCT). Bone Marrow Transplant 2000;25:957-64.
160. Bierman PJ, Vose JM, Anderson JR, Bishop MR, Kessinger A, Armitage JO. High-dose therapy with autologous hematopoietic rescue for follicular low-grade non-Hodgkin's lymphoma. J Clin Oncol 1997;15:445-50.
161. Cervantes F, Shu XO, McGlave PB, Ramsay NK, Miller WJ, Kersey JH, et al. Autologous bone marrow transplantation for non-transformed low-grade non-Hodgkin's lymphoma. Bone Marrow Transplant 1995;16:387-92.
162. Conde E, Sierra J, Iriondo A, Domingo A, Garcia Larana J, Marin J, et al. Prognostic factors in patients who received autologous bone marrow transplantation for non-Hodgkin's lymphoma. Report of 104 patients from the Spanish Cooperative Group GEL/TAMO. Bone Marrow Transplant 1994;14:279-86.
163. Vaishampayan U, Karanes C, Du W, Varterasian M, al Katib A. Outcome of relapsed non-Hodgkin's lymphoma patients after allogeneic and autologous transplantation. Cancer Invest 2002; 20:303-10.
164. Pettengell R. Autologous stem cell transplantation in follicular non-Hodgkin's lymphoma. Bone Marrow Transplant. 2002;29 Suppl 1:S1-4.
165. Carella AM, Cavaliere M, Lerma E, Ferrara R, Tedeschi L, Romanelli A, et al. Autografting followed by nonmyeloablative immunosuppressive chemotherapy and allogeneic peripheral-blood hematopoietic stem-cell transplantation as treatment of resistant Hodgkin's disease and non-Hodgkin's lymphoma. J Clin Oncol 2000;18: 3918-24.
166. Dreger P, Glass B, Seyfarth B, Humpe A, Claviez A, von Neuhoff N, et al. Reduced-intensity allogeneic stem cell transplantation as salvage treatment for patients with indolent lymphoma or CLL after failure of autologous SCT. Bone Marrow Transplant. 2000; 26: 1361-2.
167. Bernard M, Dauriac C, Drenou B, Leberre C, Branger B, Fauchet R, et al. Long-term follow-up of allogeneic bone marrow transplantation in patients with poor prognosis non-Hodgkin's lymphoma. Bone Marrow Transplant. 1999; 23:329-33.
168. Forrest DL, Thompson K, Nevill TJ, Couban S, Fernandez LA. Allogeneic hematopoietic stem cell transplantation for progressive follicular lymphoma. Bone Marrow Transplant 2002; 29:973-8.
169. Giralt S, Estey E, Albitar M, van Besien K, Rondon G, Anderlini P, et al. Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. Blood 1997;89: 4531-6.
170. Khouri IF, Saliba RM, Giralt SA, Lee MS, Okoroji GJ, Hagemeister FB, et al. Nonablative allogeneic hematopoietic transplantation as adoptive immunotherapy for indolent lymphoma: low incidence of toxicity, acute graft-versus-host disease, and treatment-related mortality. Blood 2001; 98:3595-9.
171. Kottaridis PD, Milligan DW, Chopra R, Chakraverty RK, Chakrabarti S, Robinson S, et al. In vivo CAMPATH-1H prevents graft-versus-host disease following nonmyeloablative stem cell transplantation. Blood 2000;96:2419-25.
172. van Besien K, Sobocinski KA, Rowlings PA, Murphy SC, Armitage JO, Bishop MR, et al. Allogeneic bone marrow transplantation for low-grade lymphoma. Blood. 1998;92:1832-6.
173. Robinson SP, Goldstone AH, Mackinnon S, Carella A, Russell N, de Elvira CR, et al. Chemoresistant or aggressive lymphoma predicts for a poor outcome following reduced-intensity allogeneic progenitor cell transplantation: an analysis from the Lymphoma Working Party of the European Group for Blood and Bone Marrow Transplantation. Blood 2002; 100:4310-6.
174. Del Canizo M, Amigo M, Hernandez JM, Sanz G, Nunez R, Carreras E, et al. Incidence and characterization of secondary myelodysplastic syndromes following autologous transplantation. Haematologica 2000;85:403-9.
175. van Besien K, Loberiza FR Jr, Bajorunaite R, Armitage JO, Bashey A, Burns LJ, et al. Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood 2003;102:3521-9.
176. Bierman PJ, Sweetenham JW, Loberiza FR Jr, Taghipour G, Lazarus HM, Rizzo JD, et al. Syngeneic hematopoietic stem-cell transplantation for non-Hodgkin's lymphoma: a comparison with allogeneic and autologous transplantation--The Lymphoma Working Committee of the International Bone Marrow Transplant Registry and the European Group for Blood and Marrow Transplantation. J Clin Oncol 2003; 21:3744-53.
177. Berdeja JG, Jones RJ, Zahurak ML, Piantadosi S, Abrams RA, Borowitz MJ, et al. Allogeneic bone marrow transplantation in patients with sensitive low-grade lymphoma or mantle cell lymphoma. Biol Blood Marrow Transplant 2001;7:561-7
178. Ho AY, Devereux S, Mufti GJ, Pagliuca A. Reduced-intensity Rituximab-BEAM-CAMPATH allogeneic haematopoietic stem cell transplantation for follicular lymphoma is feasible and induces durable molecular remissions. Bone Marrow Transplant 2003; 31: 551-7.
179. Mitterbauer M, Neumeister P, Kalhs P, Brugger S, Fischer G, Dieckmann K, et al. Long-term clinical and molecular remission after allogeneic stem cell transplantation (SCT) in patients with poor prognosis non-Hodgkin's lymphoma. Leukemia 2001;15:635-41.
180. Toze CL, Shepherd JD, Connors JM, Voss NJ, Gascoyne RD, Hogge DE, et al. Allogeneic bone marrow transplantation for low-grade lymphoma and chronic lymphocytic leukemia. Bone Marrow Transplant. 2000;25:605-12.
181. Davis T, Kaminski MS, Leonard JP, Hsu FJ, Wilkinson M, Wahl R, et al. Long-term results of a rrandomized trial comparing tositumomab and Iodine-131 tositumomab (BEXXAR) with tositumomab alone in patients with relapsed or refractory low-grade (LG) or transformed (T-LG) non-Hodgkin's lymphoma (NHL). Blood 2003;102: 405a-6a[abstract 1474].
182. Kaminski MS, Estes J, Zasadry KR, Francis IR, Ross CW, Tuck M, et al. Radioimmunotherapy with iodine 131 tositumomab for relapsed or refractory B-cell non-Hodgkin lymphoma: updated results and long-term follow-up of the University of Michigan experience. Blood 2000;96:1259-66.
183. Kaminski M, Leonard J, Zelenetz A, Vose J, Coleman M. Bexxar induces durable complete response in patients with relapsed (REL) and refractory (REF) low-grade (LG) or transformed (LG) non-Hodgkins lymphoma (NHL) confirmed by masked indipendent review. Ann Oncol 2002; 13[abstract 297].
184. Kaminski MS, Zelenetz AD, Press OW, Saleh M, Leonard J, Fehrenbacher L, et al. Pivotal study of Bexxar (iodine I 131 tositumomab) for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2001;19:3918-28.
185. Witzig TE, White CA, Gordon LI, Wiseman GA, Emmanouilides C, Murray JL, et al. Safety of yttrium-90 ibritumomab tiuxetan radioimmunotherapy for relapsed low-grade, follicular, or transformed non-Hodgkin's lymphoma. J Clin Oncol 2003;21:1263-70.
186. Emmanouilides CE, Witzig TE, Molina A, Gordon LE, Multani P, Wiseman GA, et al. Improved safety and efficacy of yttrium-90 ibritumomab tiuxetan radioimmunotherapy when administered as 2nd or 3rd line therapy for relapsed low-grade, follicular, and transformed B-cell non-Hodgkin's lymphoma (NHL). Proc Am Soc Clin Oncol 2003;22595[Abstract 2392].
187. Flinn IW, Witzig TE, White CA, Gordon L, Emmanouilides C, Cripe LD, et al. The Zevalin radioimmunotherapy (RIT) regimen is active in heavily pretreated, bulky, Rituximab refractory NHL. J Clin Oncol 2001;20: 286a[abstract].
188. Armitage JO, Leonard JP, Gregory SJ, Horning AD, Zelenetz AD, Kaminski MS, et al. The effectiveness of tositu-

momab and iodine I 131 tositumomab in relapsed/refractory follicular grade 1/2 and small lymphocytic non-Hodgkin's lymphoma (NHL). ASCO 2004 6573 [Abstract].
189. Gordon LI, Witzig TE, Murray JL, Czuczman MS, Emmanouilides C, Joyce RM, et al. Yttrium-90 ibritumomab tiuxetan radioimmunotherapy produces high response rates and durable remissions in patients with relapsed or refractory low grade, follicular or transformed B-cell NHL: Final results of a randomized controlled trial. ASCO 2004. 39th Annual Meeting Chicago Illinois [Abstract 2315].
190. Emmanouilides C, Witzig TE, White CA, Gordon LI, Wisemn GA, Murray JL, et al. Zevalin™ radioimmunotherapy is associated with a low infection risk. Blood 2001;98:227b-8b.
191. Bennett JM, Zelenetz AD, Press OW, Vose JM, Radford JA, Knox SJ, et al. Incidence of myelodysplastic syndromes (tMDS) and acute myeloid leukemia (tAML) in patients with low-grade non-Hodgkin's lymphoma (LG-NHL) treated with Bexxar™. Blood 2001;98:335a[Abstract].
192. Bennett JM, Kaminski MS, Leonard JP, Vose JM, Zelenetz AD, Knox SJ, et al. Assessment of treatment-related myelodysplastic syndromes and acute myeloid leukemia in patients with non-Hodgkin's lymphoma treated with Tositumomab and Iodine I 131 Tositumomab (BEXXAR(R). Blood 2005;105:4576-82.
193. Bastion Y, Sebban C, Berger F, Felman P, Salles G, Dumontet C, et al. Incidence, predictive factors, and outcome of lymphoma transformation in follicular lymphoma patients. J Clin Oncol 1997; 15:1587-94.
194. Alsabeh R. Transformation of follicular lymphoma into CD30-large cell lymphoma with anaplastic cytologic features. Am J Surg Pathol 1997;21:528-36
195. Acker B, Hoppe RT, Colby TV, Cox RS, Kaplan HS, Rosenberg SA. Histologic conversion in the non-Hodgkin's lymphomas. J Clin Oncol 1983;1:11-6.
196. Yuen AR, Kamel OW, Halpern J, Horning SJ. Long-term survival after histologic transformation of low-grade follicular lymphoma. J Clin Oncol 1995; 13:1726-33.
197. Matolcsy A. High-grade transformation of low-grade non-Hodgkin's lymphomas: mechanisms of tumor progression. Leuk Lymphoma 1999;34: 251-9.
198. Williams CD, Harrison CN, Lister TA, Norton AJ, Blystad AK, Coiffier B, et al. High-dose therapy and autologous stem-cell support for chemosensitive transformed low-grade follicular non-Hodgkin's lymphoma: a case-matched study from the European Bone Marrow Transplant Registry. J Clin Oncol 2001; 19:727-35.
199. Jantunen E, Mahlamaki E, Nousiainen T. Feasibility and toxicity of high-dose chemotherapy supported by peripheral blood stem cell transplantation in elderly patients (≥60 years) with non-Hodgkin's lymphoma: comparison with patients <60 years treated within the same protocol. Bone Marrow Transplant 2000;26:737-41.
200. Mazza P, Palazzo G, Amurri B, Cervellera M, Manna N, Fellini G, et al. Analysis of feasibility of myeloablative therapy and autologous peripheral stem cell (PBSC) transplantation in the elderly: an interim report. Bone Marrow Transplant 1999;23:1273-8.
201. Moreau P, Milpied N, Voillat L, Colombat P, Mahe B, Rapp MJ, et al. Peripheral blood stem cell transplantation as front-line therapy in patients aged 61 to 65 years: a pilot study. Bone Marrow Transplant 1998;21:1193-6.
202. Guba SC, Vesole DH, Jagannath S, Bracy D, Barlogie B, Tricot G. Peripheral stem cell mobilization and engraftment in patients over age 60. Bone Marrow Transplant. 1997;20:1-3
203. Gopal AK, Gooley TA, Golden JB, Maloney DG, Bensinger WI, Petersdorf SH, et al. Efficacy of high-dose therapy and autologous hematopoietic stem cell transplantation for non-Hodgkin's lymphoma in adults 60 years of age and older. Bone Marrow Transplant 2001; 27:593-9
204. Brenner M, Rill D, Moen R, et al. Gene-marking to trace origin of relapse after autologous bone marrow transplantation. Lancet 1993;341:85-86.
205. Apostolidis J, Gupta RK, Grenzelias D, Maloney DG, Bensinger WI, Petersdorf SH, et al. High-dose therapy with autologous bone marrow support as consolidation of remission in follicular lymphoma: long-term clinical and molecular follow-up. J Clin Oncol 2000; 18:527-36
206. Rohatiner A, Johnson P, Price C, Arnott SJ, Amess JA, Norton AJ, et al. Myeloablative therapy with autologous bone marrow transplantation as consolidation therapy for recurrent follicular lymphoma. J Clin Oncol 1994; 12:1177-84.
207. Brown JR, Yeckes H, Friedberg JW, Neuberg D, Kim H, Nadler LM, et al. Increasing incidence of late second malignancies After Conditioning with cyclophosphamide and total-body irradiation and autologous bone marrow transplantation for non-Hodgkin's lymphoma. J Clin Oncol 2005;23: 2208-14.
208. Darrington DL, Vose JM, Anderson JR, Bierman PJ, Bishop MR, Chan WC, et al. Incidence and characterization of secondary myelodysplastic syndrome and acute myelogenous leukemia following high-dose chemoradiotherapy and autologous stem-cell transplantation for lymphoid malignancies. J Clin Oncol 1994;12:2527-34.
209. Anderson JR, Vose J, Kessinger A. Myelodysplastic syndrome after autologous transplant for lymphoma. Blood 1994;84:3988-9.
210. Milligan DW, Ruiz-de-Elvira MC, Kolb HJ, Goldstone AH, Meloni G, Rohatiner AZ, et al. Secondary leukaemia and myelodysplasia after autografting for lymphoma: results from the EBMT. EBMT Lymphoma and Late Effects Working Parties. European Group for Blood and Marrow Transplantation. Br J Haematol 1999;106:1020-6.
211. Conde E, Insunza A, Lahuerta JJ, Sureda A, Caballero D, Arranz R, et al. Autologous stem cell transplantation (ASCT) in 419 patients with follicular lymphoma (FL). Blood 2002; 100:642a[Abstract 2528].
212. Wheeler C, Khurshid A, Ibrahim J, Elias A, Mauch P, Ault K, Antin J. Incidence of post transplant myelodysplasia/acute leukemia in non-Hodgkin's lymphoma patients compared with Hodgkin's disease patients undergoing autologous transplantation following cyclophosphamide, carmustine, and etoposide (CBV). Leuk Lymphoma 2001;40:499-509.
213. Lenz G, Dreyling M, Schiegnitz E, Haferlach T, Hasford J, Unterhalt M, et al. Moderate increase of secondary hematologic malignancies after myeloablative radiochemotherapy and autologous stem-cell transplantation in patients with indolent lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group. J Clin Oncol 2004; 22:4926-33.
214. Stein RS, Greer JP, Goodman S, Brandt SJ, Morgan DS, Macon WR, et al. Limited efficacy of intensified preparative regimens and autologous transplantation as salvage therapy in high grade non-Hodgkin's lymphoma. Leuk Lymphoma 2001;40:521-8.
215. Metayer C, Curtis RE, Vose J, Sobocinski KA, Horowitz MM, Bhatia S, et al. Myelodysplastic syndrome and acute myeloid leukemia after autotransplantation for lymphoma: a multicenter case-control study. Blood 2003;101:2015-23.
216. Pedersen-Bjergaard J, Andersen MK, Christiansen DH. Therapy-related acute myeloid leukaemia and myelodysplasia after high-dose chemotherapy and autologous stem cell transplantation. Blood 2000;95:3273-9.
217. Harrison CN, Gregory W, Hudson GV, Devereux S, Goldstone AH, Hancock B, et al. High-dose BEAM chemotherapy with autologous haemopoietic stem cell transplantation for Hodgkin's disease is unlikely to be associated with a major increased risk of secondary MDS/AML. Br J Cancer 1999;81: 476-83.
218. Traweek ST, Slovak ML, Nademanee AP, Brynes RK, Niland JC, Forman SJ. Clonal karyotypic hematopoietic cell abnormalities occurring after autologous bone marrow transplantation for Hodgkin's disease and non-Hodgkin's lymphoma. Blood 1994;84:957-63.
219. Abruzzese E, Radford JE, Miller JS, Vredenburgh JJ, Rao PN, Pettenati MJ, et al. Detection of abnormal pretransplant clones in progenitor cells of patients who developed myelodysplasia after autologous transplantation. Blood 1999; 94:1814-9.
220. Lillington DM, Micallef IN, Carpenter E, Neat MJ, Amess JA, Matthews J, et al. Detection of chromosome abnormalities pre-highdose treatment in patients developing therapyrelated myelodysplasia and secondary acute myelogenous leukemia after treatment for non- Hodgkin's lymphoma. J Clin Oncol 2001;19:2472-81.
221. Horning S, Cherry A, Bangs D, Negrin R, Blume K. Serial assessment of marrow cytogenetics after autologous transplantation of follicular lymphoma. Blood. 2000;96:406a[Abstract].
222. Apostolidis J, Foran JM, Johnson PW, Norton A, Amess J, Matthews J, et al. Patterns of outcome following recurrence after myeloablative therapy with autologous bone marrow transplantation for follicular lymphoma. J Clin Oncol 1999;17:216-21.
223. Hosing C, Saliba RM, McLaughlin P, Andersson B, Rodriguez MA, Fayad L, et al. Long-term results favor allogeneic over autologous hematopoietic stem cell transplantation in patients with refractory or recurrent indolent non-Hodgkin's lymphoma. Ann Oncol 2003; 14:737-44
224. Verdonck LF. Allogeneic versus autologous bone marrow transplantation for

refractory and recurrent low-grade non-Hodgkin's lymphoma: updated results of the Utrecht experience. Leuk Lymphoma 1999;34:129-36.
225. Verdonck L, Dekker A, Lokhorst H, Petersen E, Nieuwenhuis H. Allogeneic versus autologous bone marrow transplantation for refractory and recurrent low-grade non-Hodgkin's lymphoma. Blood 1997;90:4201-5.
226. Brice P, Simon D, Bouabdallah R, Belanger C, Haioun C, Thieblemont C, et al. High-dose therapy with autologous stem-cell transplantation (ASCT) after first progression prolonged survival of follicular lymphoma patients included in the prospective GELF 86 protocol. Ann Oncol 2000;11:1585-90
227. Freedman AS, Neuberg D, Mauch P, Soiffer RJ, Anderson KC, Fisher DC, et al. Long-term follow-up of autologous bone marrow transplantation in patients with relapsed follicular lymphoma. Blood 1999;94:3325-33.
228. Horning SJ, Negrin RS, Hoppe RT, Rosenberg SA, Chao NJ, Long GD, et al. Highdose therapy and autologous bone marrow transplantation for follicular lymphoma in first complete or partial remission: results of a phase II clinical trial. Blood 2001;97:404-9.
229. Schouten HC. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP Trial. J Clin Oncol 2003;21:3918-27.
230. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995;333:1540-5.
231. Salles G, Moullet I, Charlot C, Thieblemont C, Bouafia F, Dumunet C, et al. In vivo purging with rituximab before autologous peripheral blood progenitor cell 8PBPC) transplantation in lymphoma patients. Blood 1999;94 Suppl 1:141a[Abstract].
232. Krishnan A, Bhatia S, Arber DA, Arber DA, Niland JC, Nademanee A, et al. Predictors of therapy-related leukemia and myelodysplasia following autologous transplantation for lymphoma: an assessment of risk factors. Blood 2000; 95:1588-93.
233. Williams C, Goldstone A, Pearce R, Philip T, Hartmann O, Colombat P, et al. Purging of bone marrow in autologous bone marrow transplantation for non-Hodgkin's lymphoma: a case-matched comparison with unpurged cases by the European Blood and Marrow Transplant Lymphoma Registry. J Clin Oncol 1996; 14:2454-64.
234. Cao TM, Horning S, Negrin RS, Hu WW, Johnston LJ, Taylor TL, et al. High-dose therapy and autologous hematopoietic-cell transplantation for follicular lymphoma beyond first remission: the Stanford University experience. Biol Blood Marrow Transplant 2001;7:294-301.
235. Stockerl-Goldstein KE, Horning SJ, Negrin RS, Chao NJ, Hu WW, Long GD, et al. Influence of preparatory regimen and source of hematopoietic cells on outcome of autotransplantation for non-Hodgkin's lymphoma. Biol Blood Marrow Transplant 1996;2:76-85.
236. Seyfarth B, Kuse R, Sonnen R, Glass B, Schmitz N, Dreger P. Autologous stem cell transplantation for follicular lymphoma: no benefit for early transplant? Ann Hematol 2001;80:398-405.
237. Gutierrez-Delgado F, Maloney DG, Press OW, Golden J, Holmberg LA, Maziarz RT, et al. Autologous stem cell transplantation for non-Hodgkin's lymphoma: comparison of radiation-based and chemotherapy-only preparative regimens. Bone Marrow Transplant 2001;28:455-61.
238. Winter JN, Inwards D, Erwin W. Phase I trial combining 90Y Zevalin and high-dose BEAM chemotherapy with hematopoietic progenitor cell transplant in relapsed or refractory B-Cell NHL Blood 2001;98:677a-8a[Abstract].
239. Gopal AK, Gooley TA, Maloney DG, Petersdorf SH, Eary JF, Rajendran JG, et al. High-dose radioimmunotherapy versus conventional high-dose therapy and autologous hematopoietic stem cell transplantation for relapsed follicular non-Hodgkin's lymphoma: a multivariable cohort analysis. Blood 2003; 102:2351-7.
240. Liu SY, Eary JF, Petersdorf SH, Martin PJ, Maloney DG, Appelbaum FR, et al. Follow-up of relapsed B-cell lymphoma patients treated with iodine-131-labeled anti-CD20 antibody and autologous stem-cell rescue. J Clin Oncol 1998;16: 3270-8.
241. Flinn IW, Diehl LF, Garrett E, Goodrich A, Carter-Brookins D, Jones RJ, et al. Rituximab and peripheral blood stem cell transplantation produces durable remissions in patients with low grade and mantle cell lymphoma. Session Type. Blood 2003;102:247a-8a[abstract 869].
242. Brugger W. Improving outcomes in transplantation. Semin Oncol 2002; 29: 23-26
243. Benekli M, Hahn T, Shafi F, Qureshi A, Alam AR, Czuczman MS, et al. Effect of Rituximab on peripheral blood stem cell mobilization and engraftment kinetics in non-Hodgkin's lymphoma patients. Bone Marrow Transplant 2003;32:139-43.
244. Buckstein RJ, Imrie KR, Spaner D, Mangel J, Tomkins K, Crump M, et al. Autologous stem cell transplant combined with Rituximab for relapsed follicular lymphoma achieve prolonged clinical and molecular remission. Blood 2001;98:680a[Abstract].
245. Buckstein R, Imrie K, Spaner D, Potichnyj A, Robinson JB, Nanji S, et al. Stem cell function and engraftment is not affected by "in vivo purging" with Rituximab for autologous stem cell treatment for patients with low-grade non-Hodgkin's lymphoma. Semin Oncol 1999;26 Suppl 14:115-22.
246. Flinn IW, O'Donnell PV, Goodrich A, Vogelsang G, Abrams R, Noga S , et al. Immunotherapy with Rituximab during peripheral blood stem cell transplantation for non-Hodgkin's lymphoma. Biol Blood Marrow Transplant 2000;6:628-32.
247. Voso MT, Pantel G, Weis M, Schmidt P, Martin S, Moos M, et al. In vivo depletion of B cells using a combination of high-dose cytosine arabinoside/mitoxantrone and rituximab for autografting in patients with non-Hodgkin's lymphoma. Br J Haematol 2000;109:729-35.
248. Hirt C, Dolken G. Quantitative detection of t(14;18)-positive cells in patients with follicular lymphoma before and after autologous bone marrow transplantation. Bone Marrow Transplant 2000;25:419-26.
249. Johnson P, Price C, Smith T, Cotter FE, Meerabux J, Rohatiner AZ, et al. Detection of cells bearing the t(14;18) translocation following myeloablative treatment and autologous bone marrow transplantation for follicular lymphoma. J Clin Oncol 1994;12:798-805.
250. Ladetto M, Corradini P, Vallet S, Benedetti F, Vitolo U, Martelli M, et al. High rate of clinical and molecular remissions in follicular lymphoma patients receiving high-dose sequential chemotherapy and autografting at diagnosis: a multicenter, prospective study by the Gruppo Italiano Trapianto Midollo Osseo (GITMO). Blood; 2002;100:1559-65.
251. Darby AJ, Johnson PWM. Molecular remission and non-Hodgkin's lymphoma. Best Practice Res Clin Haematol 2002;15:549-62.
252. Michallet M, Bilger K, Garban F, Attal M, Huyn A, Blaise D, et al. Allogeneic hematopoietic stem-cell transplantation after nonmyeloablative preparative regimens: impact of pretransplantation and posttransplantation factors on outcome. J Clin Oncol 2001;19: 3340-9.
253. Martino R, Caballero MD, Canals C, Simon JA, Solano C, Urbano-Ispizua A, et al. Allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning: results of a prospective multicentre study. Br J Haematol 2001;115:653-9.
254. Korbling M, Anderlini P. Peripheral blood stem cell versus bone marrow allotransplantation: does the source of hematopoietic stem cells matter? Blood 2001;98:2900-8.
255. Kyriakou CA, Milligan D, Chopra R, Craddock C, Chakraverty R, Mahendra P, et al. Outcome of non-myeloablative stem cell transplantation for NHL Is dependent on histology: good for Patients with low grade disease and poor for those with high grade lymphoma. Blood 2001;98:414a [abstract 1737].
256. Perez-Simon JA, Kottaridis PD, Martino R, Craddock C, Caballero D, Chopra R, et al. Nonmyeloablative transplantation with or without alemtuzumab: comparison between 2 prospective studies in patients with lymphoproliferative disorders. Blood 2002; 100:3121-7.
257. Gregory SA, Leonard JP, Knox SJ, Zelenetz AD, Armitage J, Kaminski M. The iodine I-131 tositumomab therapeutic regimen: Summary of safety in 995 patients with relapsed/refractory low grade (LG) and transformed LG non-Hodgkin's lymphoma (NHL). ASCO 2004; [Abstract 6732].
258. Vose JM, Wahl, Saleh M, Rohatiner AZ, Knox SJ, Radford JA, et al. Multicenter phase II study of iodine-131 tositumomab for chemotherapy-relapsed/refractory low-grade and transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2000;18:1316-23.
259. Leonard JP, Zelenetz AD, Vose JM, Radford JA, Wahl RL, Rohatiner A, et al. Iodine 131 tositumomab for patients with low-grade or transformed low-grade NHL: complete response data. Blood 2000;96:728a [abstract].
260. Horning SJ, Younes A, Jain V, Kroll S, Lucas J, Podoloff D, Goris M. Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after ritux-

imab. J Clin Oncol 2005;23:712-9.
261. Murray J, Witzig T, Wiseman G, Czuczman M, Lynch J, Kornmehl E. Zevalin therapy can convert peripheral Blood BCL-2 Status from positive to negative in patients with low-grade, follicular or transformed non-Hodgkin's lymphoma (NHL). ASCO 2000; 77[Abstract].
262. Kaminski M, Tuck M, Estes J, Kolstad A, Ross CW, Zasadny K et al. 131I Tositumomab therapy as intial treatment for follicular lymphoma. N Engl J Med 2005;352:441-9.
263. Armitage JO, Dick FR, Corder MP. Diffuse histiocytic lymphoma after histologic conversion: a poor prognostic variant. Cancer Treat Rep 1981;65: 413-8.
264. Riccioni R, Galimberti S, Cervetti G, Fazzi R, Caracciolo F, Pertini M. Oral cyclophosphamide therapy for patients with residual or relapsed indolent-type lymphoma after initial treatment for aggressive lymphomas. A sub-group of patients with apparent transformed indolent lymphoma. Leuk Lymphoma 2002;43:1803-6.
265. Ostrow SS, Diggs CH, Sutherland JC, Gustafson J, Wiernik PH. Nodular poorly differentiated lymphocytic lymphoma: changes in histology and survival. Cancer Treat Rep 1981;65: 929-33.
266. Friedberg J, Neuberg D, Gribben J, Mauch P, Anderson K, Soiffer R, et al. Autologous bone marrow transplantation following histologic transformation of indolent B cell non-Hodgkin's lymphoma. Blood 1998;92: 727a [abstract].
267. Chen CI, Crump M, Tsang R, Stewart AK, Keating A. Autotransplants for histologically transformed follicular non-Hodgkin's lymphoma. Br J Haematol 2001;113:202-8.
268. Berlung A, Enblad G, Carlson K, Glimelius B, Hagberg H. Long-term follow-up of autologous stem-cell transplantation for follicular and transformed follicular lymphoma. Eur J Haematol 2000;65:17-22.
269. Friedberg JW, Neuberg D, Gribben JG, Mauch P, Anderson KC, Soiffer RJ, et al. Autologous bone marrow transplantation after hy histologic transformation of indolent B cell malignancies. Biol Blood Marrow Transplant 1999;5: 262-8.
270. Foran JM, Apostolidis J, Papamichael D, Norton AJ, Matthews J, Amess JA, et al. High-dose therapy with autologous haematopoietic support in patients with transformed follicular lymphoma: a study of 27 patients from a single centre. Ann Oncol 1998;9:865-9.
271. Lerner RE, Burns LJ. Transformed lymphoma: an Achilles' heel of non-Hodgkin's lymphoma. Bone Marrow Transplant 2003;31:531-7.
272. Bolwell B, Kalaycio M, Andersen S, Goormastic M, McBeeM, Kuczkowski E, et al. Autologous peripheral blood progenitor cell transplantation for transformed diffuse large-cell lymphoma. Leuk Lymph 2000;1:226-31.
273. Le Gouill S, Moreau P, Morineau N, Harousseau JL, Milpied N. Tandem high-dose therapy followed by autologous stem-cell transplantation for refractory or relapsed high grade non-Hodgkin's lymphoma with poor prognosis factors: a prospective pilot study. Haematologica 2002;87:333-4
274. Robinson SP, Goldstone AH, Mackinnon S, Carella A, Russell N, de Elvira CR, et al. Chemoresistant or aggressive lymphoma predicts for a poor outcome following reduced-intensity allogeneic progenitor cell transplantation: an analysis from the Lymphoma Working Party of the European Group for Blood and Bone Marrow Transplantation. Blood 2002; 100:4310-6
275. Juckett M, Rowlings P, Hessner M, Keever-Taylor C, Burns W, Camitta B, et al. T cell-depleted allogeneic bone marrow transplantation for high-risk non-Hodgkin's lymphoma: clinical and molecular follow-up. Bone Marrow Transplant 1998;21:893-9.
276. Schimmer AD, Jamal S, Messner H, Keating A, Meharchand J, Huebsch L, et al. Allogeneic or autologous bone marrow transplantation (BMT) for non-Hodgkin's lymphoma (NHL): results of a provincial strategy. Ontario BMT Network, Canada. Bone Marrow Transplant 2000;26:859-64.
277. Dhedin N, Giraudier S, Gaulard P, Esperou H, Ifrah N, Michallet M, et al. Allogeneic bone marrow transplantation in aggressive non-Hodgkin's lymphoma (excluding Burkitt and lymphoblastic lymphoma): a series of 73 patients from the SFGM database. Societ Francaise de Greffe de Moelle. Br J Haematol 1999;107:154-61.
278. Przepiorka D, van Besien K, Khouri I, Hagemeister F, Samuels B, Folloder J, et al. Carmustine, etoposide, cytarabine and melphalan as a preparative regimen for allogeneic transplantation for high-risk malignant lymphoma. Ann Oncol 1999;10:527-32.
279. Karsan A, Gascoyne RD, Coupland RW, Shepherd JD, Phillips GL, Horsman DE. Combination of t(14;18) and a Burkitt's type translocation in B-cell malignancies. Leuk Lymphoma 1993; 10:433-41. J Clin Oncol 1999;17: 1558-67.
280. Macpherson N, Lesack D, Klasa R, Horsman D, Connors JM, Barnett M, Gascoyne RD. Small noncleaved, non-Burkitt's (Burkitt-Like) lymphoma: cytogenetics predict outcome and reflect clinical presentation. J Clin Oncol 1999; 17:1558-67.
281. www.agreecollaboration.com (accessed on February 2005)
282. Shiffman RN, Shekelle P, Overhage M, Slutcky J, Grimshaw J, Deshpande AM. Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. Ann Intern Med 2003; 139:493-8.
283. Zelenetz AD, Hoppe RT; NCCN Non-Hodgkin's Lymphoma Practice Guidelines Panel. NCCN: non-Hodgkin's lymphoma. Cancer Control 2001 Nov-Dec;8 (6 Suppl 2): 102-13. Updated at http://www.nccn.org/physician_gls/f_guidelines.html accessed on February 20, 2004.
284. Hiddemann W; European Society for Medical Oncology. ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of newly diagnosed follicular lymphoma. Ann Oncol 2003;14:1163-4.