Treatment of follicular lymphoma and mantle cell lymphoma

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Follicular lymphoma

Follicular lymphoma (FL) is the second most frequent lymphoma after diffuse large B-cell lymphomas and represents 20% to 25% of all lymphomas. It is characterised by a proliferation of CD10+ B-cells that bear the (14;18) translocation or *bcl*-2 gene rearrangement. If the proliferation corresponds initially to small cleaved cells (centrocytes), with time it evolves to larger cells (centroblasts) and this is not always associated with a different outcome. The proportion of centroblasts and the size of centrocytes vary in different lymph nodes from the same patient. At diagnosis, the disease usually involves several lymph nodes around the body and a truly localised disease is seen in only 20% to 25% of the patients. Involved sites are predominantly lymph nodes, spleen and bone marrow, and occasionally peripheral blood or extranodal sites. Extranodal site involvement, other than the bone marrow or blood, is often associated with a more aggressive disease or a histological progression.

Prognostic parameters

Standard prognostic parameters have been described and recognised by the whole community for aggressive lymphomas [1], but, until recently, such prognostic parameters were not isolated in FL patients. Each large group has described its version of parameters characterising patients who should be treated. If similarities exist between these different definitions, they are not identical. The most widely used is the one described by the GELA (Groupe d'Etude des Lymphomes de l'Adulte) in its successive trials [2]. Patients who needed to be treated were characterised by a large tumour burden, a poor performance status (PS $>$ 1) or the presence of B symptoms. High tumour burden was defined by the presence of at least one of the following parameters: one tumour larger than 7 cm or more than 3 lymph nodes larger than 3 cm, large splenomegaly, serous effusion or compressive tumour, above normal lactic dehydrogenase (LDH) level, and β2-microglobulin level $\geq$ 3 mg/l. The absence of all these parameters defines a very indolent course, and thus patients for whom immediate intervention is not required.

Some other prognostic parameters have been described. Recently, a large international cooperative study noted 12 pre-treatment characteristics as being important for survival: gender, age group, Ann Arbor stage, bone marrow involvement, spleen involvement, number of nodal areas involved, number of extra-nodal involvement sites other than bone marrow, B symptoms, anaemia, lymphocytopenia, presence of absence of thrombocytopenia, and serum LDH level [3]. This allowed a new index to be described, the Follicular International Prognostic Index (FLIPI), based on age, disease stage, LDH level, haemoglobin level, and number of nodal sites. The International Prognostic Index (IPI) described for aggressive lymphomas may be applied with the same prognostic significance to FL patients [4]. These 2 indexes discriminate well between good-risk and poor-risk patients.

The (14;18) translocation is the landmark of follicular lymphoma and, with the improvement of molecular techniques, it may be found in nearly 100% of the patients even if the classical *bcl*-2 gene rearrangement is only found in 60% to 70% of the cases. The disappearance of cells with *bcl*-2 rearrangement from the blood or bone marrow was associated with a better outcome in several studies [5]. However, false-positive and false-negative results may be observed in some studies, and, so far, no standard validation procedure has been described to validate the results. Currently, this biological marker is not used to define the treatment of a given patient.

For years, it was debated whether follicular lymphoma with a large cell component has a clinical behaviour distinct from other FL. In large-scale retrospective analyses, the survival of FL patients was identical, whatever the percentage of large cells. It was recently demonstrated that the percentage of

large cells is not important, but that poor outcome was related to the presence of a predominant diffuse infiltration (> 50%) [6]. After one or several relapses, sometimes at the time of diagnosis, the disease transforms into a more aggressive lymphoma characterised by a proliferation of large non-cleaved cells or Burkitt-like cells. At this time, patients usually have a large tumour mass, B symptoms, and a high LDH level; and the duration of the response to any treatment is short, except for patients treated with high-dose therapy and autotransplant.

FL patients must be allocated to different treatments based on the presence or absence of adverse prognostic parameters.

Treatment

Localised disease. Approximately 20% of FL patients have localised disease with no bulky tumour mass. In such patients, targeted radiotherapy achieves complete remission in over 95% of cases and relapse-free 10-year survival in 50% of cases. However, the probability of cure is very low because there is no plateau in the survival curve and most of the patients tend to relapse. The benefit of radiation therapy (RT) over a short chemotherapy has not been demonstrated in any prospective trial. No randomised data exists to support adjuvant chemotherapy. Nevertheless, data from a large phase II study from MD Anderson Cancer Center suggests that combined chemotherapy and RT can produce progression-free survival results that are far superior to historical series, with survival at 10 years being approximately 20% superior to radiation alone. This may change in the future with the use of monoclonal antibodies.

Patients with low tumour mass. Around 30% of the patients present with disseminated disease and an absence of adverse prognostic parameters. In this setting, treatment is not mandatory and can be deferred until there is evidence of progression, i.e. when adverse prognostic factors become apparent. Spontaneous regression occurs, but complete regression is seen in less than 5% of patients. Most patients may have stable disease for 1–4 years depending on the proportion of large cells. However, the disease eventually progresses in most patients, resulting in death (40–70% of cases after histological transformation) after a median survival of 8–10 years. Prospective studies have shown that treatment at diagnosis did not prolong survival in these patients with a low tumour burden [7]. For this reason, we recommend that these patients do not start treatment at diagnosis, that they be monitored until they develop progressive disease with emergence of adverse prognostic factors, and only then be treated as described later (Fig. 1). This delayed strategy is currently the best treatment

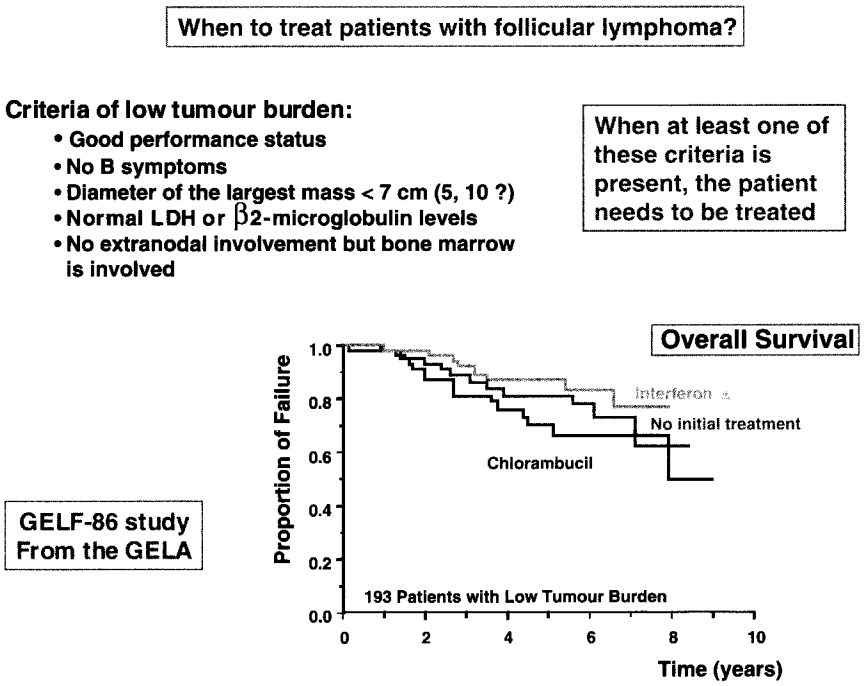

Fig. 1. This figure lists the criteria used by the GELA (Groupe d'Etude des Lymphomes de l'Adulte) for defining a low tumour burden and shows the survival of patients included in the randomised study in which the patients were included if they did have any of these criteria. *A contrario*, it means that patients should be proposed to be treated when at least one of these criteria is present. LDH, lactate dehydrogenase.

option to offer these patients, but this may change in the future, particularly with the development of monoclonal antibodies.

Standard treatment. At least 50% of FL patients need to be treated at diagnosis because of the presence of one or several adverse prognostic factors. In these patients, several studies have shown that a doxorubicin-containing regimen allowed a better and quicker response, but was not associated with a longer survival in comparison with CVP or high-dose chlorambucil. Several randomised studies have been published comparing the addition of interferon to chemotherapy in naïve patients or interferon versus no further treatment in responding patients. Several of these studies showed a benefit in terms of time to progression or overall survival for the arm with interferon, but not all of them. However, the combination of chemotherapy plus interferon was associated with the best results ever obtained in follicular lymphoma patients [8]. Nearly all the studies that showed a benefit in terms of time to progression or of survival have only accrued patients with adverse prognostic parameters, have treated these patients with a doxorubicin-containing regimen or a mitoxantrone-containing regimen, and have used a higher dose of interferon for a longer duration. Until recently, the only improvement demonstrated in randomised studies was the addition of interferon to a doxorubicin-containing regimen, but this treatment was not adopted by all physicians because of the toxicity of interferon.

Several studies compared prospectively or historically fludarabine or fludarabine-containing regimens with doxorubicin-containing regimen. Fludarabine alone has less efficacy than a doxorubicin-containing regimen plus interferon [9]. Fludarabine associated with mitoxantrone or cyclophosphamide or both is associated with better results than fludarabine alone, but a much greater toxicity. These regimens were never compared to the association of a doxorubicin-containing regimen plus interferon. Because of the interest of monoclonal antibodies in this lymphoma, no further studies will be organised in the future to respond to these pending questions.

Monoclonal antibodies. Treatment with monoclonal antibody (MAb), conjugated or unconjugated, had allowed response rates over 50% in relapsing FL patients, but these drugs have never been tested in any randomised study, even if they are used in every patient with FL [10]. When treated with MAb alone, nearly all these relapsing patients progressed after a period of 12 to 18 months, but half of them responded to further courses of rituximab. In relapsing patients, radiolabelled MAb seemed to be associated with a higher response rate, but a not-so-different time to next progression [11]. In first-line patients, phase II studies with rituximab alone or in combination with chemotherapy have showed good results, but until the presentation of randomised studies, this could not be recommended as standard therapy for FL patients. In phase II studies, combination of chemotherapy and rituximab showed better results than rituximab alone, particularly in untreated patients. The combination of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) plus rituximab was particularly powerful and the results of ongoing randomised studies may change our philosophy for treating follicular lymphoma patients, if they confirm the results of phase II trials. However, neither the right regimen to combine with rituximab nor the right combination has been described. The list of currently available MAb is presented in Table 1. Only rituximab (MabThera®, Rituxan®) is currently licensed for the treatment of FL and at time of relapse or refractoriness to standard therapy. The advantages of rituximab over interferon are the better tolerance of the treatment and the higher efficacy when used alone, even if this was not demonstrated by any randomised study.

Currently, rituximab alone or in combination with

Table 1
Major monoclonal antibodies used in the treatment of patients with follicular lymphoma

Antibody	Antigen	Conjugate	Proven efficacy	Authors
Rituximab (MabThera, Rituxan)	CD20	None	Follicular lymphoma in relapse DLCL in combination with chemotherapy	Maloney Coiffier
Alemtuzumab (Campath)	CD52	None	Chronic lymphocytic leukaemia	Keating Lundin
Epratuzumab (Lymphocide)	CD22	None	In testing	Leonard
Hu1D10	HLA–DR	None	In testing	Leonard
Ibritumomab tiuxetan (Zevalin)	*CD20*	*Y-90*	*Progression after rituximab*	*Gordon Witzig*
Tositumomab (Bexxar)	*CD20*	*I-131*	*Progression after rituximab*	*Kaminski Vose*

Radiolabelled antibodies are in italics. DLCL, diffuse large B-cell lymphoma.

chemotherapy is being tested in several settings in randomised studies. However, none of these studies is yet completed and no definitive data are available to propose any recommendations. Preliminary results have shown that the combination of rituximab with chemotherapy seemed the best treatment ever used in first-line patients or in relapsing patients [12]. One study showed that in relapsing patients, the response rate, but not the event-free survival, was better with ibritumomab tiuxetan (Zevalin®) compared with rituximab [13].

High-dose therapy with autologous transplant has been used for several years in relapsing patients with either purged bone marrow cells or non-purged peripheral blood cells. It has enabled a significant prolongation of time-to-treatment failure over that obtained with standard treatments. In large single-centre trials, it seems associated with a longer time to next progression than the one observed with standard therapy used in first- or second-line. However, some questions persist, such as the nature of the best conditioning regimen, particularly the place of total body irradiation (TBI), the necessity of purging autologous cells, and when to intensify.

Whether these results will be reproducible in untreated patients has been tested in two randomised trials that are not yet published. However, these studies were done some years ago, before the era of monoclonal antibodies, and the putative advantage of high-dose therapy over standard therapy will have to be reanalysed with the inclusion of MAb in the standard treatment of these patients, particularly the fact that rituximab allows the purging of lymphoma cells in blood and bone marrow.

FL in transformation is a really aggressive disease and if the patients may respond to standard progression, time to next progression and survival after the histological transformation is usually shorter than one year. Selected patients with histological transformation, particularly those whose transformation occurs early in the course of their disease and who remain chemosensitive, may experience prolonged survival after HDT [14].

Allogeneic transplant. Allogeneic transplant has advantages over autologous transplant of inducing a graft-versus-lymphoma effect in combination with the killing of the lymphoma cell by high-dose chemotherapy. Its use is prevented by its higher toxicity profile. The so-called mini-transplant with reduced-dose conditioning regimen has less toxicity than chemotherapy and, thus, may be used in older patients. It has the same anti-lymphoma effect due to a small, controlled, graft-versus-host and lymphoma reaction [15]. No prospective study has compared allogeneic transplant and HDT with autologous stem cell support. Most presented studies are feasibility or phase II studies where the bias of patient selection hampers the analysis of the results [16]. Some studies have tried to compare both modalities on a large-scale basis, retrospective analysis of registry, and have concluded that allogeneic transplant is associated with a higher mortality secondary to treatment, a lower relapse rate and a similar survival [17].

Other therapeutic modalities. Vaccination against lymphoma cells is a promising treatment that has been under development for many years with very few available results because of the difficulties of developing vaccines [18]. The patient's lymphoma cells are used to construct a vaccine comporting an adjuvant such as GM–CSF (granulocyte macrophage colony stimulating factor) or a toxin. Currently, if the immunological effect is demonstrated with appearance of antibodies directed against lymphoma cells, no therapeutic results have been presented [19]. This therapeutic modality is quite expensive and time-consuming, preventing its use on a large-scale basis or in a randomised trial.

Antisense oligonucleotides have the ability to selectively block disease-causing genes, thereby inhibiting production of disease-associated proteins. Targeting the initiating codon of the *bcl*-2 gene decreases both cell viability and bcl-2 protein expression in FL cell lines that overexpress bcl-2 [20]. In the future, antisense therapy followed by chemotherapy might overcome chemoresistance to provide effective therapy for a range of malignancies.

***bcl*-2 Gene monitoring**. Until recently, *bcl*-2-rearranged cells persisted in the blood and bone marrow of FL patients, and this persistence may induce the recurrence of lymphoma after HDT [5]. Trials with *ex vivo* purge and selection of CD34+ cells were not convincing because they resulted in only a small log decrease of the *bcl*-2-rearranged cells [21]. The clinical response to rituximab treatment was associated with a clearance of the *bcl*-2-rearranged cells in the blood and bone marrow, even for patients in PR (partial response) with persisting increased lymph nodes. Thus, stem cell harvest after rituximab therapy may collect purer haematopoietic stem cells without or with less detectable *bcl*-2-rearranged cells. However, the results have not yet been presented for the relapse rate after this treatment. Several modalities of rituximab administration are currently being tested, but the combination of chemotherapy and rituximab at the time of salvage treatment some weeks before the harvest is probably the most interesting modality.

Relapsing patients. Because FL is incurable in the vast majority of patients, nearly all will relapse.

At the time of relapse, treatment may be delayed until the disease is menacing, often more rapidly than in first-line patients, but most of the patients need to be treated during the year after the first manifestation of the relapse. Here too, no standard exists for the best modality. Rituximab is certainly a very interesting drug, alone or in combination with chemotherapy. Other monoclonal antibodies have activity after failure of rituximab.

The most difficult point is to define when a relapsing patient must be offered HDT with autologous transplant [22]. Only studies with historical comparison are available, but most of them allowed one to conclude that HDT should be offered at the time of the patient receiving his/her second chemotherapy regimen, whatever the number of courses of rituximab. For patients with transformed lymphoma, only HDT has been associated with a long event-free survival [14]. However, the patient must respond to a salvage regimen before being able to move on to such intensification.

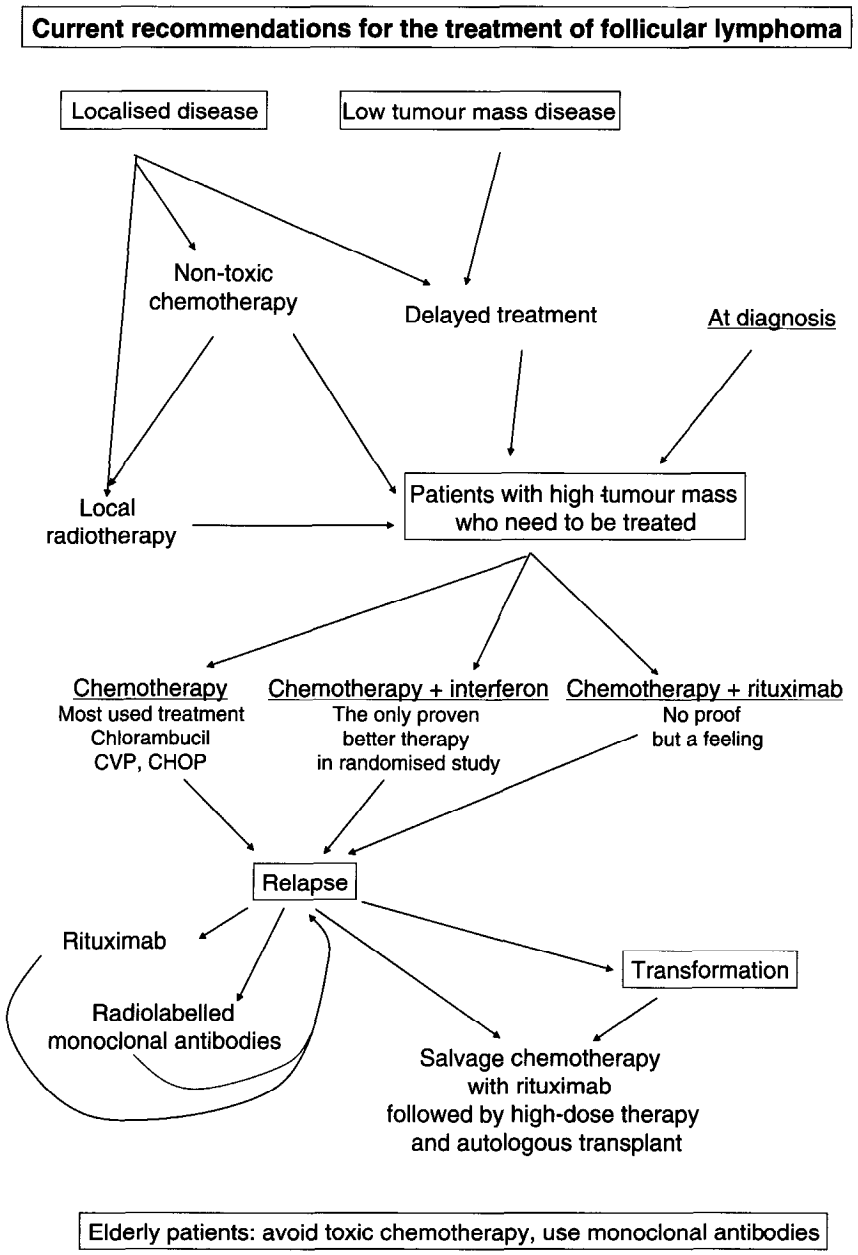

Fig. 2. Current recommendations for the treatment of patients with follicular lymphoma. CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone. CVP: cyclophosphamide, vincristine, prednisone.

Current recommendations for treating patients with follicular lymphoma (Fig. 2)

Patients with non-bulky localised disease may either be treated with local radiotherapy, alone or following a short non-toxic chemotherapy, or be included in a delayed strategy. Regarding overall survival, both modalities are probably similar. Patients with a low tumour mass should be offered delayed therapy.

Patients with high tumour mass, either at diagnostis or after delayed treatment, need to be treated. The old standard was chemotherapy with high-dose chlorambucil, CVP (cyclophosphamide, vincristine, prednisone) or CHOP. Combination of chemotherapy plus interferon was the only regimen to be associated with better results in randomised trials and, thus, will be the standard arm with which any new combination must be compared. Because of the efficacy of monoclonal antibodies in phase II trials, they will be part of new combinations, but their exact place, the type of combination, the duration of the treatment, or the interest in any maintenance therapy have not yet been settled. To include such patients in prospective randomised trials is certainly the best a physician may do for his/her patient.

At relapse, re-treatment with monoclonal antibodies is the first choice. Salvage chemotherapy with rituximab followed by high-dose therapy with autotransplant is currently reserved for relapsing patients or at transformation.

Mantle cell lymphoma

Mantle cell lymphoma (MCL) represents one of the worst lymphomas because of its refractoriness to any treatment that has been developed. The disease has many facets in its histological, clinical, or outcome aspects. The initial presentation is characterised by a slow increase of lymph node volume making it a real indolent lymphoma. At diagnosis, most patients have disseminated disease with enlarged lymph nodes, bone marrow and blood involvement, splenomegaly, and often extranodal sites such as colic or Waldeyer ring tumours. The incidence of this lymphoma seems similar in the US and Europe, representing 8% of the non-Hodgkin's lymphomas. Because of this low incidence, very few prospective clinical trials exist, making it impossible to define recommendations for the treatment of these patients.

Treatment

Usual treatments, such as chlorambucil or multidrug regimens with or without doxorubicin, are associated with a low CR rate, close to 30%, even if most patients reach a PR with the initial treatment. Whatever the treatment and the response, median time to progression does not exceed 18 months and median survival is around 3 years [23]. New combination with high-dose aracytine seemed to be associated with higher response rates than CHOP-like regimens. Fludarabine was tested in phase II studies in naive or relapsing patients, but it showed only a moderate activity. Very few patients with MCL have been included in the reported trials that combined fludarabine with different drugs. Results of different non-randomised trials with interferon therapy have confirmed its possible advantage as a maintenance or consolidation therapy in MCL patients who responded to initial therapy.

Monoclonal antibodies, particularly rituximab, have activity in MCL patients [24,25]. In two European studies *de novo* or relapsed patients were treated with rituximab and 35% of them responded to this treatment. Among the responding patients, one-third reached a CR and two-thirds a PR. Rituximab combined with CHOP allowed a higher response rate with 50% CR [26]. However, in these studies if the response rate was high with rituximab alone or in combination with chemotherapy, median duration of response was not really longer compared with what was described with chemotherapy alone.

No randomised trial of HDT with autotransplant has been reported and only preliminary conclusions may be drawn from small phase II studies or retrospective analyses. Most of the patients received cyclophosphamide plus TBI as the conditioning regimen but the dose of radiation varied in the different studies. Few procedure-related deaths were reported, but most of these patients relapsed after the transplant. This high relapse rate is evident when the median follow-up of the treated patients was longer than 2 years. The failure of high dose therapy with autologous transplant in MCL patients is related to the difficulty of purging contaminant lymphoma cells from the harvest. Rituximab has allowed the *in vivo* purge of blood and bone marrow even when patients did not reach a complete remission. Thus, studies of *in vivo* purging with first line treatment combining chemotherapy plus rituximab followed by HDT and autotransplant are ongoing and preliminary results showed an improvement over historical controls. However, the definitive results are not known.

Current recommendations for treating patients with mantle cell lymphoma

Mantle cell lymphoma is a frustrating and increasingly frequent problem for haematologists and oncologists. Chemotherapy combined with rituximab and followed by high-dose therapy with autotransplant may be the best treatment to currently propose to these patients if they are younger than 65 years. For older patients, no standard is available; the combination of chemotherapy plus rituximab is associated with the best results and should be used outside of clinical trials. As in FL patients, rituximab or radiolabelled MAb as maintenance therapy may have a role that has yet to be demonstrated.

References

1 The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J M 1993, 329: 987–994.

2 Decaudin D, Lepage E, Brousse N, et al. Low-grade stage III–IV follicular lymphoma: Multivariate analysis of prognostic factors in 484 patients: A study of the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 1999, 17: 2499–2505.

3 Solal-Celigny P, Roy P. Follicular Lymphoma International Prognostic Index (FLIPI). Ann Oncol 2002, 13 (suppl 2): 18.

4 Bastion Y, Coiffier B. Is the international prognostic index for aggressive lymphoma patients useful for follicular lymphoma patients? J Clin Oncol 1994, 12: 1340–1342.

5 Lopez-Guillermo A, Cabanillas F, McDonnell TI, et al. Correlation of *bcl*-2 rearrangement with clinical characteristics and outcome in indolent follicular lymphoma. Blood 1999, 93: 3081–3087.

6 Hans CP, Weisenburger DD, Vose JM, et al. A significant diffuse component predicts for inferior survival in grade 3 follicular lymphoma, but cytologic subtypes do not predict survival. Blood 2003, 101: 2363–2367.

7 Brice P, Bastion Y, Lepage E, 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. J Clin Oncol 1997, 15: 1110–1117.

8 Rohatiner AZ, Gregory W, Peterson B, et al. A meta-analysis of randomized studies evaluating the role of interferon alpha as treatment for follicular lymphomas. Proc ASCO 2002, 21: 264a.

9 Coiffier B, Neidhardt-Berard EM, Tilly H, et al. Fludarabine alone compared to CHVP plus interferon in elderly patients with follicular lymphoma and adverse prognostic parameters: A GELA study. Ann Oncol 1999, 10: 1191–1197.

10 Grillo-Lopez AJ, Hedrick E, Rashford M, Benyunes M. Rituximab: Ongoing and future clinical development. Semin Oncol 2002, 29: 105–112.

11 Goldenberg DM. Targeted therapy of cancer with radiolabeled antibodies. J Nucl Med 2002, 43: 693–713.

12 Hiddemann W, Forstpointner R, Fiedler F, et al. The addition of rituximab to combination chemotherapy with fludarabine, cyclophosphamide, mitoxantrone (FCM) results in a significant increase of overall response as compared to FCM alone in patients with relapsed or refractory follicular (FCL) and mantel cell lymphomas (MCL). Results of a prospective randomized comparison of the German Low Grade Study Group (GLSG). Blood 2001, 98 (suppl 1): 844a.

13 Witzig TE, Gordon LI, Cabanillas F, et al. 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, 20: 2453–2463.

14 Williams CD, Harrison CN, Lister TA, 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: 727–735.

15 Appelbaum FR. Haematopoietic cell transplantation as immunotherapy. Nature 2001, 411: 385–389.

16 Khouri IF, Saliba RM, Giralt SA, 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: 3595–3599.

17 Schimmer AD, Jamal S, Messner H, et al. Allogeneic or autologous bone marrow transplantation (BMT) for non-Hodgkin's lymphoma (NHL): results of a provincial strategy. Bone Marrow Transplantation 2000, 26: 859–864.

18 Bendandi M. Anti-idiotype vaccines for human follicular lymphoma. Leukemia 2000, 14: 1333–1339.

19 Timmerman JM, Czerwinski DK, Davis TA, et al. Idiotype-pulsed dendritic cell vaccination for B-cell lymphoma: clinical and immune responses in 35 patients. Blood 2002, 99: 1517–1526.

20 Jansen B, Zangemeister-Wittke U. Antisense therapy for cancer — the time of truth. Lancet Oncol 2002, 3: 672–683.

21 Schouten HC, Kvaloy S, Sydes M, Qian W, Fayers PM. The CUP trial: A randomized study analyzing the efficacy of high dose therapy and purging in low-grade non-Hodgkin's lymphoma (NHL). Ann Oncol 2000, 11: 91–94.

22 Brice P, Simon D, Bouabdallah R, 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: 1585–1590.

23 Weisenburger DD, Vose JM, Greiner TC, et al. Mantle cell lymphoma, a clinicopathologic study of 68 cases from the Nebraska Lymphoma Study Group. Am J Hematol 2000, 64: 190–196.

24 Foran JM, Rohatiner AZS, Cunningham D, et al. European phase II study of rituximab (chimeric anti-CD20 monoclonal antibody) for patients with newly diagnosed mantle-cell lymphoma and previously treated mantle-cell lymphoma, immunocytoma, and small *B-cell lymphocytic lymphoma. J Clin Oncol 2000, 18: 317–324.

25 Foran JM, Cunningham D, Coiffier B, et al. Treatment of mantle-cell lymphoma with Rituximab (chimeric monoclonal anti-CD20 antibody): Analysis of factors associated with response. Ann Oncol 2000, 11: 117–121.

26 Howard OM, Gribben JG, Neuberg DS, et al. Rituximab and CHOP induction therapy for newly diagnosed mantle-cell lymphoma: Molecular complete responses are not predictive of progression-free survival. J Clin Oncol 2002, 20: 1288–1294.